The Goulstonian Lectures

ON

SOME CONSIDERATIONS ON

THE NATURE OF DIABETES MELLITUS

Delivered before the Royal College of Physicians of London on March 16th, 21st, and 23rd, 1905

BY

W. CECIL BOSANQUET, M.A., M.D. Oxon.

F.R.C.P. Lond.

ASSISTANT PHYSICIAN TO CHARING CROSS HOSPITAL AND TO THE BROMPTON HOSPITAL FOR CONSUMPTION AND DISEASES OF THE CHEST; FORMERLY FELLOW OF NEW COLLEGE, OXFORD.

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LECTURE 1.

Delivered on March 16th.

Mr. President and Gentlemen,—I must first thank you for the honour which you have conferred upon me by inviting me to deliver these lectures—an honour which I very highly appreciate but which has nevertheless proved to me a source of considerable embarrassment. Indeed, the hesitation which I at first felt about undertaking the duties of the post has since been strengthened into an assured conviction that it was only too fully justified. It must always, I think, be a task of great difficulty for one of the junior Fellows of this College to deliver a lecture before his seniors who must needs be better acquainted with all the facts of medicine than he; and the difficulty is specially great in the case of one who, like myself, is attached only to a comparatively small hospital where material for study is much less than that available at our larger institutions. Fortunately, it has been wisely arranged that the Goulstonian lecturer should deal mainly with pathology—the theoretical side of disease—rather than with clinical phenomena or treatment. And as pathology is a constantly advancing science it may be profitable at times to review some of the facts recently ascertained and the hypotheses put forward to explain them, if only to elicit the truth that there are still very lamentable gaps in our knowledge upon all medical subjects and that the continual stream of medical writings rather conceals than fills in these deficiencies.

In choosing for my subject the nature of diabetes I am conscious that I may appear guilty of more than ordinary presumption, inasmuch as it is one which has been most exhaustively investigated by one of the senior Fellows of this College who has made the subject his own and attained

therein a position of authority which is recognised throughout the civilised world. Dr. F. W. Pavy, by his careful and illuminating researches into the physiology of the assimilation of carbohydrate food, has thrown light into some of the dark corners which abound in the field of diabetes. Yet he himself would readily, I think, admit that the nature of the disease is still far from being finally determined; that there are many problems awaiting solution and scope for much further research and speculation.

As it was the orginal intention of the founder of these lectures that they should be devoted to demonstration of morbid anatomy, so I hope to deal mainly with the relation of the disease to structural alterations in the organs, recognisable after death, and to discuss the reasons which exist for associating any one of them causally with the existence of diabetes. But in recent days all the great advances in pathology have been made by means of experiments on living animals and I would refer also to the results of some such researches which have appeared to give rise to conditions resembling the human malady. Lastly, there have in the last few years been promulgated theories connected with the resistance of the body to parasitic invasion which have involved conjectures as to some of the processes by which food is assimilated by the tissues. It may be not wholly uninteresting, though unfortunately premature so far as certainty is concerned, to speculate as to the bearing of these theories on the pathology of diabetes.

Definition of Diabetes.

In the discussion of any matter it is advisable to make some attempt to define the terms which we are using and it may be useful at the outset to consider for a moment what it is that we mean when we speak of diabetes mellitus. It is true that definition is impossible in science before we know all about the phenomenon which we wish to define, and for this reason final definitions are practically unattainable, except in abstract reasoning such as mathematics, since knowledge of natural phenomena and their causes is constantly growing. In the field of medicine we can see the process of modification of our ideas in accordance with the advance of knowledge constantly at work. Thus originally, as Allbutt has pointed out, diseases were groups of symptoms which recurred in association sufficiently frequently to constitute a definite idea. No doubt scientifically minded persons early realised that these groups were the outward and visible signs of altered conditions of the body, but of the nature of the condition present in each case they had no knowledge. Later it was found that certain structural alterations were invariably associated with the symptoms of many diseases and these underlying physical conditions assumed more and more im-

portance in the connotation of the name of the disease. In these instances the stage of morbid anatomy had been reached. Later still we have acquired a knowledge of the causes of certain diseases and of some at least of the means by which they produce their characteristic symptoms. This knowledge is only definite in the case of some of the infective diseases, such as tetanus or tuberculosis, in which we can isolate the pathogenic bacteria, investigate the poisons which they generate, and unravel to some extent their modes of action and the defensive reactions of the infected organism.

In the case of many diseases we are still in the stage of morbid anatomy ; examples are seen in the various anæmias, of which nothing more is known than the alterations in the constitution of the blood. In diabetes we have hardly as yet attained to even this stage of knowledge. Attempts have, indeed, been made to show that changes are invariably to be found after death in the pancreas, of which I hope to say more in my next lecture ; but at present there is no consensus of opinion as to the constancy of these changes—or rather, it has been pointed out there are many cases of the disease in which no alterations in this organ can be demonstrated, so that there seems a danger of even this association—the most hopeful prospect of establishing the disorder on an anatomical basis—proving elusive. Yet we know that it is impossible for perversions of function to occur in normal circumstances without coexistent alteration of structure, since function is merely structure undergoing change, as was pointed out by G. H. Lewes many years ago ; so that if the conditions of the cell remain the same and its structure the same the function must continue the same likewise. In other words, all functional defects must arise from structural lesions, whether these are gross, or microscopical, or ultra-microscopical.

In the case of diabetes the gradual alteration in the connotation of the name can be easily recognised. In the earliest times, when the name was first invented, there can be no doubt that all conditions accompanied by polyuria were classed together ; to all the comparison of the patient to a syphon transmitting a continual stream of water was equally applicable. The discovery of the existence of sugar in some cases of the disease was made late in the history of medicine. In the East it was unknown till some hundreds of years after the commencement of the present era and in the West it remained undiscovered till the time of our countryman, Willis, towards the end of the seventeenth century who noted the sweet taste of the urine. The actual proof of the presence of sugar was afforded a little later by Dobson. The spirit of Western inquiry, as contrasted with Eastern apathy, is well exemplified by the rapid growth of information on the subject which followed Willis's discovery. The writer of an anonymous medical treatise on diabetes, published at Oxford in 1745, notes that the disease was then attracting much attention and discussion ; and up

to the present time an ever-increasing volume of writings has centred round its pathology.

Since the discovery of sugar in the urine and the resulting separation of saccharine from insipid diabetes and from other causes of polyuria further steps in the subdivision of the subject have been made. In the first place, it is recognised that all cases in which there is sugar in the urine are not diabetes mellitus. Glycosuria is now known to be a possible accompaniment of many diseases having no apparent connexion with the malady with which the condition was first associated. Cerebral injuries, many nervous conditions, Graves's disease, and other maladies may be accompanied by glycosuria, yet we do not call them diabetes. We have then to inquire what criterion exists for the identification of true diabetes as apart from such conditions of symptomatic glycosuria and the question is not easily answered. It would seem that our only grounds in most cases for asserting that a patient is suffering from diabetes are the amount and the persistence of the glycosuria. It is manifest that such criteria are unsatisfactory. Taken separately each would be fallacious. A considerable quantity of sugar may exist at any one time in the urine apart from diabetes. I well remember a patient having been brought into Charing Cross Hospital one night comatose, with a fairly large amount of sugar in the urine. He was supposed to be suffering from diabetic coma and was treated somewhat energetically by bleeding and infusion of saline solution. At the necropsy the case was found to be one of cerebral hæmorrhage, yet the quantity of sugar in the urine had been considerable. On the other hand, if permanency of the glycosuria is to be the necessary condition for distinguishing diabetes we should be unable to admit that a case could ever be cured, nor could the condition be satisfactorily diagnosed until the patient was dead. The old Greek proverb that we should call no one fortunate till he was dead, because a reverse of luck might at any time occur, was perhaps a wise piece of advice, but it would be unsatisfactory in medical practice, where it would sometimes seem that the assignment of a name to a disease is only less gratifying to the patient than its cure or alleviation. We cannot base the definition of a disease upon its insusceptibility of cure. And if we ask how long the glycosuria must last before we can call a case diabetes it is not easy to give an answer. Yet in diabetes, in the absence of any ascertained morbid anatomical changes invariably associated with the disease, we seem compelled to rely for grounds of diagnosis and even of definition upon the amount and persistence of the glycosuria. How unsatisfactory this is will be readily apparent when we consider what our position would be if we knew only the fact of the existence of albumin in the urine in certain conditions, without possessing any knowledge of structural changes in the kidneys, or if we were similarly limited in our knowledge in the presence of hæmaturia. We might perhaps get as far as recognising

the existence of mild "functional" conditions in which the disorder cleared up without difficulty and grave cases of organic disease which rapidly went downhill—and that is about as far as we have got in the study of diabetes—but exact knowledge would be quite impossible.

As a sign of the present unsatisfactory results of attempts to define diabetes it is sufficient to indicate the conditions at present grouped under the term. Tyson gives the following varieties of glycosuria, to all of which the name diabetes is sometimes applied, arranged according to their causes: (1) alimentary glycosuria due to imperfect assimilation of carbohydrates; (2) glycosuria due to over-production of glucose from the hepatic glycogen; (3) vaso-motor glycosuria, owing to too rapid passage of glucose through the liver, without being converted into glycogen; (4) defective oxidation of glucose in the system (this form he associates with pancreatic and suprarenal disease); and (5) incurable diabetes, in which proteid is converted into sugar, including the fixed proteid of the tissues (this is accompanied by acid intoxication.) The group of disorders included in this list is manifestly made up of a heterogeneous collection of but slightly connected conditions which only our ignorance of the nature of the phenomena leads us to classify under the same term. It seems possible that some at least of the obscurity in which the subject of diabetes is wrapped arises from a failure to distinguish the disease from conditions which simulate it and that we must here apply the old maxim *divide et impera* and subdivide the group before we can extend the realm of knowledge.

Alimentary and composite diabetes.—In this direction an important division has been made in the subject by the distinction drawn between two forms or stages of diabetes mellitus—between cases on the one hand in which apparently the sugar which emerges in the urine is derived entirely from the carbohydrate materials contained in the food and cases in which, on the other hand, some of it, at all events, is formed by breaking down of the tissues of the patient. To these the names of "alimentary" and "composite" diabetes have been assigned by Pavy. This brings us to one of the remarkable points about the disease to which it is, perhaps, curious that more attention has not been paid. In many instances the first stage of the malady is signalised only by an alimentary glycosuria—that is, by an apparent inability to assimilate any considerable quantity of carbohydrate food. In the later stages the same patient not only cannot assimilate this kind of food but he also suffers from an actual breaking down of his own tissues into sugar. It is difficult to believe that the two conditions are the same in any way or that one can really pass into the other. To suppose that the presence of excess of sugar in the system acts poisonously and leads in time to a destruction of the body cells, of such a nature that the very poison

at work is one of the products of the disintegration, is absolutely contrary to all analogy in vital chemistry. In cases in which special bodies are formed in the animal economy in response to the injection of toxic materials we find that the substance is of such a nature as to neutralise the effects of the poison, as in the process of immunising animals against certain vegetable poisons (abrin, ricin, &c.) or against the toxins of bacteria. In the case of the commoner poisons, mineral and organic, no such antitoxic power is, indeed, exhibited; but no instance of the actual poison itself being formed by the cells as a result of its own action is known. It is unlikely, then, on general grounds that sugar should form a special exception and cause breaking down of the cell protoplasm into sugar. There is indeed, no proof, so far as I am aware, that it is actually a poisonous substance. It appears to be a normal constituent of the blood, though existing there in very small quantities; and in default of direct evidence we should suppose that the only evil effects which it would be likely to exert would be by increasing the density of the plasma and thereby altering the osmotic pressure relatively to the surrounding tissues and to the formed elements of the blood.

The facts just mentioned—namely, the existence of alimentary and composite forms of diabetes—appear to constitute the ground-work of our knowledge of the disease, in which everything else is largely a matter of speculation and conjecture. We know that in the early stages of many cases of diabetes it is possible entirely, or almost entirely, to prevent the appearance of sugar in the urine by diminishing the amount of carbohydrate material given in the food. The inference seems necessarily to be that the sugar in the urine is derived directly or indirectly from the matter ingested. On the other hand, we know that in severe cases and in the later stages of many cases which originally appeared to be instances of alimentary diabetes the sugar in the urine persists in the absence of all carbohydrate food—nay, more, in conditions of starvation, in the absence of all food of any kind whatever. Here it is equally necessary to believe that the sugar is derived from the breaking down of some substance forming part of the living body. These being the two most securely established facts with regard to diabetes it is, I venture to think, to the explanation of them and of their mutual relationship that it is most important to direct attention in any attempt to explain the nature of the disease. It is comparatively useless to explain one phenomenon without explaining the other simultaneously; any hypothesis which fails to embrace both together is defective *ab initio*.

It is necessary, then, to look about for some explanation of the phenomena of diabetes capable of embracing both alimentary and composite cases. Now we know that sugar may appear in the urine in many conditions which are not

diabetes as a result of ingestion of saccharine food. On the other hand, we know of no other condition in which there is an internal formation of sugar by disintegration of materials existing in the body. Further, this latter feature is characteristic of the developed disease, when all the conditions are presumably best marked. It appears, then, reasonable to regard this internal formation of sugar as the essential characteristic of the disease and to turn our attention specially to this rather than to the alimentary factor. So far as I can judge the reverse procedure has generally been adopted in studying the disease and the result has been to leave what I believe to be the most striking feature of diabetes mellitus unexplained.

We have to ask, then, Is it possible to formulate any hypothesis, consistent with what we know of the phenomena of diabetes, which shall explain alimentary diabetes in terms, if I may so express it, of composite diabetes? Now it may be taken as admitted that the sugar which appears in the urine is merely filtered off from the blood—in other words, that glycosuria presupposes glychæmia. The sugar present in the blood may arise in any one of several ways—from increased ingestion of sugar in the food or from increased formation in the body, or from diminished elimination or assimilation of the amount normally present. In alimentary glycosuria it would seem that the sugar reaches the blood by absorption from the intestine; in composite diabetes it seems that some of it comes from the breaking-down of the tissues. Have we any means of assuring ourselves that in either case only one process is at work? In the case of the latter condition it seems certain that there is no alimentary element coexisting, since in starvation no food is taken. In the former case the same exclusion is not possible. It is true that in alimentary glycosuria cutting off the supply of carbohydrate food will stop or diminish the exit of sugar in the urine, but this does not necessarily constitute a proof that such food is the sole source of the sugar. The coexistence of an internal source of sugar formation cannot be excluded. Indeed, Seegen states that dieting in some instances may decrease the sugar which appears in the urine but not that which exists in the blood. Now the amount of sugar present in the blood is the resultant of the forces which respectively pour sugar into it and remove it, and sugar may be removed by assimilation as well as by excretion. It is conceivable that the body may have the power of dealing with a certain quantity of this substance but not with more than a definite amount. If the whole of this amount is formed within the body it is clear that any further quantity entering from the intestine will appear in the urine; while if a large proportion, but not the whole, of the amount is formed within the body then the quantity of sugar which can enter from the intestine without causing glycosuria will be so much less than in a normal person who either forms no internal sugar or only a com-

paratively small amount. I venture to think that this possibility is at least worth considering as involving less difficulty in the explanation of the conversion of a case of alimentary glycosuria into one of composite diabetes than is involved in the supposition of the onset of a new pathological process. In favour of an internal formation of sugar in diabetes may be quoted the observations of Kolisch that in bad cases a carbohydrate diet may cause no increase in the amount of sugar present in the urine, which may vary from day to day quite independently of the food taken. If such a conception were admissible a certain amount of clearness would be gained for a definition of diabetes which would consist in an increased internal formation of sugar. In mild cases this would merely diminish the amount of sugar which could be absorbed from the alimentary canal without appearing in the urine ; as the case grew graver and more internal secretion was formed, so the patient's tolerance for carbohydrate food would diminish ; and finally, the amount of internal sugar would be so great as to appear in the urine even in the absence of any alimentary supply.

It is not necessary to suppose that the amount of sugar which can be dealt with by the tissues without appearing in the urine is the same in all persons. Thus von Noorden found that of two healthy men one was capable of assimilating 150 grammes of glucose administered to him, while the other exhibited slight glycosuria when thus treated. Probably if enough sugar were given at once everyone would excrete some of it in the urine. Those who cannot deal with so much as average persons are the alimentary glycosurics ; but there is no reason why they should develop into diabetics apart from an increased internal sugar formation, and as a fact they do not all so develop. The power of assimilating sugar varies even in the same person in different circumstances, as a man who is working hard will eliminate less sugar in his urine, as the result of an overdose of this substance, than one who is at rest (Breul). Authors appear to differ as to whether carbohydrate food, other than sugar itself, can produce alimentary glycosuria in healthy persons. Theoretical considerations would appear to be on the side of Naunyn and others who affirm this possibility, since it is fairly established that a certain proportion of starchy food is converted into sugar in the alimentary canal (Ellenberger and Hoffmeister). In pathological conditions, such as fevers and alcoholism, it has been actually proved by Strauss that glycosuria may result from the ingestion of starchy food.

Causation.

Leaving for the present the question of the essential nature of diabetes, we may turn our attention to the causation of the disease. With regard to the causes which determine the onset of diabetes nothing new seems to have

been revealed by recent research. We may not now agree with Avicenna that the most important of these causes is the eating of quinces, or with Trnka de Krzowitz that "aquosi potus ac praeprimis tepidi abusus haud difficultcr diabetem inducit,"[1] any more than with the supposition of the Rabbi Moyses that the drinking of Nile water was the most potent cause of the malady as he saw it in Egypt, but our positive knowledge is not much greater than that of early writers. The association of the disease with alcoholic habits was noticed by our forefathers in the medical profession. Dolæus attributes the onset of diabetes to drinking cyder and Willis to indulging in Rhenish wine, and there seems to be no doubt that alcoholism may play a part in its causation.

Another poison to which some importance has been attributed in the causation of diabetes is tobacco. Stern states that not only does the excessive use of this narcotic protract the duration of an alimentary glycosuria and increase the quantity of glucose in the urine but that it seems to transform slight chronic glycosuria into severe diabetes. He attributes the action of tobacco to the absorption of small doses of carbonic oxide in the process of smoking, sufficient to induce a chronic intoxication with this substance. This theory seems scarcely probable; for, although it is known that poisoning with carbonic oxide may be accompanied by glycosuria, one would think that the amount of this gas absorbed by the mucous membrane of the mouth would be insignificcnt. It is only in the case of those who inhale the smoke that such a cause would appear likely to be operative. Perhaps some of the deleterious effects attributed to cigarette smoking may result in this way; but I do not know of any observations tending to connect diabetes with this form of indulgence in tobacco more than with any other. Lorand notes that some of his diabetic patients confessed to being large smokers of cigars.

The presence in the urine of glycuronic acid—a near ally of sugar—has been observed after intoxication with a large number of substances: phosphoric acid, phosphorus, lactic acid, hydrochloric acid, strychnine, curare, arsenic, butyl-chloral hydrate, morphine, hydrocyanic acid, chloroform, and turpentine (Sydney Martin). To the form of diabetes which follows phloridzin poisoning and the injection of suprarenal extract I shall refer later.

The influence of heredity is perhaps now more fully recognised than was formerly the case. Thus, Tyson puts the hereditary cases down as one quarter of the whole number and other writers at an even higher figurc; and with heredity we must class the racial incidence of diabetes which seems to affect a larger percentage of the population among the Jews and Oriental peoples than among Europeans.

[1] This appears to refer to polyuria a potu, not to saccharine diabetes.

The greater liability of Jews than of other races to suffer from diabetes has indeed been denied by Pollatschek, and statistics on the subject are liable to be fallacious, but on the whole the fact seems well established. Thus Lorand has collected statistics from his own native town, in which there are 20,000 inhabitants; of these 3000 are Jews. He finds that diabetes is rare among the Christian population but so common among the Jews that there is scarcely a family of any size which has not among its members some sufferer from this malady. This same writer has investigated the question whether the children of diabetic parents are liable to suffer from alimentary glycosuria and thinks that the question can be answered in the affirmative—a consideration which may lend some further support to the belief in the hereditary character of the disease. But the evidence adduced is not quite convincing as to the existence of this phase of heredity in any large number of instances.

In spite of the well-established fact of the appearance of diabetes as a sequel of an attack of some infectious disease, such as enteric fever, influenza, or diphtheria, little evidence exists which seems in any way to point to an infective cause of diabetes itself—that is to say, there is nothing to indicate that it is the direct effect of a toxin formed by a pathogenic bacterium. The experiments of Charrin and Carnot, in which diabetes was produced by injection of cultures of micro-organisms into the pancreatic duct, must be explained on the ground of the production of a pancreatitis rather than as proving the origin of diabetes from the direct effects of toxins. The action of syphilis as a cause of diabetes is probably exerted in the same direction. Schmitz examined the records of 4389 diabetic patients and among them he found only four married couples; from this it would appear that the disease is not communicated from one individual to another. On the other hand, some writers maintain that conjugal infection in diabetes is not at all rare. The evidence has been recently collected by Hutinet who considers that the infection may be conveyed by the saliva; he admits, however, that this form of diabetes is less severe and more amenable to treatment than other kinds. General experience hardly bears out the contention that the malady is infectious.

Lastly, much attention has been directed to the influence of the nervous system in the causation of diabetes. On the one hand, overwork and consequent exhaustion may apparently induce the disease, as in the case of the youth long ago recorded by Boerhaave, who applied himself to his studies night and day, keeping himself awake by continual potations of tea and coffee. (Noctes diesque studiis incumbebat: somnum arcebat continua pocillatione theae atque caffeae.) This cultivation of the intellectual faculties to the neglect of hygienic principles was followed by the onset of diabetes. To this as an example of diabetes from overwork it might perhaps be objected that the tea and coffee

drunk may have acted as poisons so as to bring the case into the toxic category, but subsequent experience seems to support the belief that mental strain may be a factor in inducing the disease. The incidence of diabetes upon the Jews has been by some attributed to the anxieties incident to the callings which they tend to adopt. Sudden shock and excitement have also been quickly followed by the onset of diabetes—*pathemata animi, præsertim terror*, as Trnka de Krzowitz phrases it; and present-day observation bears out the dicta of our predecessors in this respect.

Injuries to the head are more often followed by temporary glycosuria than by lasting diabetes but the latter is said to ensue occasionally. Von Oordt noted the presence of alimentary glycosuria in many cases of cerebral disease and Haedke observed this phenomenon in 15 cases out of 25 suffering from shock. Hirschfeld found that the glycosuria seen in cases of injury to the skull was only transitory but Lenné states that in certain instances it may remain permanent.

Experimentally many varieties of injury to the nervous system may produce glycosuria. Besides Bernard's "puncture" and his operation of galvanising the central ends of the cut vagi, destruction of the pons and of the posterior crura cerebri, section of the optic thalami, section of the medulla and of the cervical cord, extirpation of the cervical sympathetic, and other lesions have been followed by glycosuria. Stimulation of the depressor nerve has had the same effect and even section of the sciatic has done the same. Sciatica itself has been stated to cause diabetes but it is at least as probable that the nerve lesion was caused by the general disease as that the opposite sequence took place. An experiment illustrating the effect of nervous influence upon the excretion of sugar is seen in the experience that if a cat be merely fastened down upon the operating table, without any further injury, sugar at once appears in the urine, the so-called "*Fesselungsdiabetes*" of the Germans (Boehme and Hoffmann.)

Connected with the question of the nervous causation of diabetes is the discovery that glycosuria is common among the insane. It is said to occur more frequently in patients suffering from depressive forms of mental disease than among the more active varieties, which would suggest that in such cases there may be a failure either in the power of utilising sugar in the tissues or in the formation of some necessary secretion rather than an active production of sugar such as would seem to occur in the other nervous conditions which have just been mentioned. We must also bear in mind the hereditary nature of diabetes and its apparent tendency to appear in the offspring of neurotic stocks, other members of which have exhibited signs of more or less marked mental disease.

On the other hand, it is certain that only a small number of those persons who are exposed to the action of the causes

just enumerated—continued hard work, shocks, and injuries —suffer from diabetes in consequence, and it is equally certain that the disease often occurs without the aid of any of these exciting causes. It is legitimate, I think, to question the reality of the causal nexus in some at least of the cases attributed to mental factors. It is difficult to be sure that we are not confusing *post hoc* with *propter hoc* in many such instances. Thus in the case of injuries and shocks it is to be borne in mind that these accidents cause patients, previously healthy in their own estimation, to seek medical advice. The urine will then be examined, and whether a temporary traumatic glycosuria be found or a pre-existing diabetes be discovered the case is likely to be looked upon as one of diabetes following injury. Again, in cases of diabetes which come under notice with the disease already developed the onset may be wrongly attributed by the sufferer, when questions are asked, to one or other of the nervous causes mentioned, and he may hence be classified as an instance of nervous diabetes when the malady was really due to some entirely different cause. There are at least few hospital patients who have not suffered from some injury in their past lives and who are not only too ready to associate any subsequent ailment with such an accident, just as every child belonging to this class who is ill has always had a fall to which maladies of the most varied description can be assigned. Hence I am inclined to think that a certain amount of scepticism is justifiable as to many, at all events, of the cases attributed to such causes.

With a view to estimate as far as possible the frequency with which the various causes are at work in cases of diabetes, or at least in cases so classified—for as previously suggested I think that, with only one symptom to guide us, many different conditions are grouped under this term—I have looked up the notes of such cases of the disease as have been treated in Charing Cross Hospital in recent years. It must be admitted that hospital patients are not an ideal class in which to investigate the matter. Such as they are I have found notes of 80 cases, of which 56 were males and 24 females (a ratio of 7 to 3).

To take first the class of causes just mentioned I found that in only two cases was the onset of the disease attributed to worry and anxiety, while in one case a shock and in one a fall were assigned as causes (5 per cent.). The most important antecedent, so far as could be gathered from a consideration of the histories of the patients, was alcoholism, which was a precedent condition, if not a cause, in no less than 13 cases, or 16 per cent.; but we must remember that it is a common failing and may be only accidentally associated. Syphilis had certainly occurred previously in six cases and probably in four others, making 12½ per cent. in which it might be assigned as a cause of the malady. Gout was an association in five instances. If Toogood's observations as to the causation of gout among the

poor are to be relied upon these cases also might be attributed to the effects of indulgence in alcohol. With regard to heredity, there were six cases (two females and four males) in which other members of the patients' families had suffered from diabetes. The most striking instance was that of a man, aged 50 years, who had two brothers and one sister either suffering from or dead from diabetes. In each of the other instances only one other member of the family had been affected. In four cases (two males and two females) there was a family history of insanity or nervous disease. Taking them altogether, heredity was only discoverable as a possible causal factor in 12½ per cent. of the whole number, a much smaller proportion than is assigned to this cause by the writers whom I have previously mentioned. In the great majority of the cases no explanation of the onset of the disease was given by the sufferers. It had come on insidiously and as far as could be gathered spontaneously. Here, perhaps, I may remark upon the large number of instances among these cases in which complaint was made of abdominal pain—generally epigastric or hypochondriac. In one or two instances intestinal disturbances, such as diarrhœa and vomiting, had preceded the apparent onset of the diabetes sufficiently closely to attract the patient's notice and in three other cases jaundice had occurred at some previous period. These features may not be without interest in view of the possible connexion of diabetes with pancreatic disease.

Morbid Anatomy.

I now turn to the morbid anatomy of the disease, the changes found in the different organs of the body in those who have died from diabetes. Ever since Claude Bernard's great discovery of the existence of glycogen in the liver and of the possibility of causing this substance to be discharged into the blood in the form of sugar by nervous action, the liver has received the greatest amount of attention in relation to the pathology of diabetes mellitus. Yet it can hardly be denied that the result has been on the whole disappointing. It must have seemed at first that there was at length a prospect of solving the mystery of this disease which had remained "a marvel" since the time of Aretæus (*θωῦμα τὸ διαβήτεω πάθος*). But although it seems certain that many cases of glycosuria, especially those which ensue as results of nervous lesions, are referable to this mode of causation, we are apparently as far as ever from explaining on this basis the nature of diabetes. It even seems legitimate to wonder whether we have not been unduly hypnotised by the phenomena of glycogenesis and led to concentrate our attention upon a side issue.

The facts ascertained with regard to the presence of glycogen in various tissues seem to point to its constituting a reserve of nutriment for actively growing cells. Thus it

is found in the cells of tumours, in germinal tissues, in the proliferating membrane of hydatid cysts, and sometimes in leucocytes. It appears to be associated with activity in the cells which contain it. May it not be the case that it is stored up by the liver cells when it, or some forerunner of it, reaches them from the food, as a fuel for their own activity which is evidently great and manifold, rather than as a reserve upon which the body at large may draw? Pavy's researches seem to show that the blood of the hepatic vein is no richer in sugar than that of the rest of the blood instead of containing more sugar as it should do if the liver were constantly furnishing sugar for the use of the body cells elsewhere. In short, the function of the liver as normally a distributer of sugar to the rest of the body is at present an unverified hypothesis.

Post-mortem examination of persons dead from diabetes reveals two main changes in the liver. In a certain proportion of cases this organ is found fatty. Thus many years ago Mead considered a "steatomatous" condition characteristic of the liver in diabetes and this phenomenon has often been noted since. But it is not invariable; indeed, it is rather the exception than the rule to find it present. In a majority of cases the liver is slightly enlarged, firm in consistency, and hyperæmic. The general impression derived from a consideration of these features is that the liver is an organ which has been working hard; the appearances do not suggest a morbid state. A peculiar lesion of the liver in diabetes has, indeed, been described by Fischer who found in a case of this disease appearances suggesting a growth of fine fibrous tissue running between the cells and columns of cells; this was quite unlike ordinary cirrhosis, either of the fine or the coarse variety, being only visible microscopically and then only on careful observation. After finding this appearance in one case of diabetes Fischer examined all the sections of liver tissue which he had by him and found among them two specimens presenting the same peculiarity. On referring to the notes of the cases from which they were taken he discovered that both of these specimens were from cases of diabetes. In one case which I examined the liver cells in certain places stained badly and here and there I noticed an appearance in these degenerate areas suggestive of the condition recorded by Fischer; it gave the impression of a cement substance between the cells which had somehow been rendered visible. So far this discovery has not been confirmed by other observers and it is difficult to connect it in any way with the causation of the disease as in Fischer's case there was no sign of injury to the liver cells.

Frogs deprived of their livers do not show any sugar in the urine as a result of the operation; nor do they exhibit diminished tolerance for carbohydrate food, with the doubtful exception of lævulose which is said to appear in the urine if administered to the animals. Indeed, the idea that it is some failure in the functions of the liver which is

the cause of diabetes is negatived by the fact that in acute yellow atrophy of this organ there is no excess of sugar in the blood or urine; nor is cirrhosis of the liver, however advanced, usually accompanied by glycosuria. Strauss in 38 cases of disease of the liver found alimentary glycosuria as a consequence of the administration of 100 grammes of dextrose in only two instances.

If, then, the liver be at fault its influence must be exerted in the direction of over-activity rather than in that of defective action. We cannot at once exclude the possibility of such a mode of causation. Nevertheless, we must bear in mind that in one form of diabetes, that known as *diabète bronzé*, to which I shall refer again later, there is advanced cirrhosis of the liver; and in one case of ordinary diabetes I myself found a very advanced and apparently active cirrhosis present. Out of 12 necropsies on diabetic subjects which I collected from our post-mortem registers, cirrhosis of the liver was present in two instances. Such a condition is hardly compatible with an excess of function. Further, if we attempt to apply the conception of an over-activity of the liver as an explanation of the cardinal facts of diabetes we shall find it inadequate. It is possible, indeed, to explain the existence of an alimentary glycosuria on the basis of a continual building up and discharge of glycogen by the liver; but it seems quite impossible to harmonise this conception with the internal formation of sugar from the body tissues, to which I have already alluded as the most characteristic feature of the disease, except on the hypothesis that the liver manufactures some poison which causes a breaking-down of the cells. This has not, so far as I know, been suggested. Naunyn's observation that acid intoxication does not occur in cases of hepatic diabetes (glycosuria ?) seems to support the view that this organ is not the seat of the primary lesion in true diebetes mellitus, since this acid poisoning is one of the most characteristic phenomena of diabetes.

The kidneys.—Attempts to explain diabetes as a disease of the kidneys have been made from the earliest times, as was indeed natural seeing the prominence of diuresis as a feature of the malady. Galen explained diabetes as owing to the kidneys attracting the urine to themselves through the vena cava, though he elsewhere explains the disease as involving a fundamental defect of metabolism (*νέκρωσις ἀμφοτέρων τῶν δυναμέων ἀλλοιώσεως τε καὶ καθελκτικῆς*). Some of the writers of the eighteenth century also favoured a renal explanation of the disease, speaking of a "laxity of the urinary passages." It is curious that one of the supporters of this latter crude view of the pathology of diabetes should criticise Galen's hypothesis as involving "fertility of imagination rather than solidity of reason."[2]

[2] Anonymous Treatise, 1745.

When we examine the actual morbid anatomy of the kidneys in diabetes we find a curiously close resemblance to the conditions met with in the liver. In the majority of cases the kidneys are large, firm, and somewhat hyperæmic; they suggest, as was the case with the liver, that they have worked their hardest to compensate the condition existing in the blood, rather than that they are the organs primarily at fault. In other cases the renal cells exhibit some fatty accumulation, such as is also seen at times in the liver, or they may contain glycogen granules. In still other instances the epithelium of the tubules has undergone hyaline degeneration. In a recent fatal case of diabetes terminating in coma, in which I examined the kidneys along with the other organs—the material being kindly placed at my disposal by Mr. P. L. Daniel, pathologist to Charing Cross Hospital—I found that practically the whole of the tubal epithelium was in a state resembling coagulation necrosis; the cells refused to take on any stain and even the nuclei could not be discovered by any staining methods. The glomeruli appeared to have escaped the morbid process to some extent and the cells and nuclei of the intertubular connective tissue were readily stained and appeared quite normal. No thrombosis of the renal vessels was found to account for this condition which must be looked upon as a result of the intoxication existing in the disease. It is natural to wonder whether the condition of the kidneys can have had anything to do with the coma with which the case terminated. It seems not impossible that in some instances at any rate, coma may be brought about as the result of a vicious circle, the kidneys being first injured by the toxic substances present in the blood which it is their function to eliminate; and this injury finally resulting in an inability to carry on their excretory function, in consequence of which failure a rapid accumulation of the poisons occurs in the system with speedily fatal issue. The sudden onset of coma appears to demand some cause of rapid accumulation of the poisons which are at work and this may perhaps be more easily explained as the result of diminished excretion than by a suddenly increased formation. The occurrence of albuminuria towards the end of cases of diabetes appears to point to the supervention of renal disease as a not very infrequent complication.

So far as the sugar present in the urine is concerned it seems satisfactorily established that the kidneys merely eliminate from the blood the sugar which is poured into it from elsewhere. There would seem to be present normally in the urine a percentage of sugar equal to that existing in the blood. One set of phenomena, and one only, has been pointed to as lending support to the theory of a renal diabetes. These phenomena are those which are seen as the result of poisoning with the substance called phloridzin. The effect of administering this drug to

animals is to produce a condition apparently exactly resembling diabetes, the condition lasting as long as the drug is continued but ceasing on its discontinuance. Not only does sugar appear in the urine but the acid intoxication characteristic of severe diabetes in human subjects is induced and death may occur in a condition resembling diabetic coma. Phloridzin is a glucoside derived from the thorn-apple and it might be suggested that it was itself converted into sugar; but, as a matter of fact, a very small dose of the substance may give rise to the excretion of many times its own weight of sugar. It is generally supposed that the glycosuria of phloridzin poisoning is produced by an increase in the permeability of the renal epithelium, so that it allows an increased quantity of sugar to pass through it. In proof of this explanation is adduced the effect of the administration of the drug to birds. In these an increased sugar content can be produced in the blood, without any sugar appearing in the urine, owing to the power possessed by the avian kidney of retaining sugar and refusing to allow its passage. If phloridzin be given to a bird in such a condition sugar immediately appears in the urine, apparently owing to injury to the renal epithelium. Other substances which injure this structure may produce the same results. The occasional glycosuria seen in cases of Bright's disease has been attributed to a similar injury to the cells of the kidneys; but it appears, on the other hand, that the existence of renal disease—either natural or experimental—may prevent the appearance of glycosuria in phloridzin poisoning (Klemperer, Richter). It is further clear that though injury to the renal epithelium may account for some of the glycosuria seen in phloridzin poisoning it cannot do so for all, since a much larger amount of sugar issues in the urine than normally exists in the blood. The drug must itself give rise to some increased formation of sugar. The acid intoxication coexisting must also be accounted for. It is noteworthy that observers differ in their findings as to the amount of sugar present in the blood in animals poisoned with phloridzin, some finding a condition of glychæmia, others a normal amount of sugar, others again a variable quantity which may exceed or fall short of the normal. It is also difficult to explain the fact that phloridzin may produce glycosuria if tranfused through a kidney locally. Pavy, Brodie, and Siau consider that phloridzin acts upon some substance already existing in the blood and converts it into sugar. It would seem necessary to suppose that it produces excess of this intermediate substance in the blood by its own action.

The administration of phloridzin is followed by intense fatty change in the liver which may be compared with the fatty condition sometimes seen in cases of diabetes. Some very interesting experiments were made by Rosenfeld to determine the source of this fat. By starving animals (dogs) for some time it is possible to get rid of practi-

cally all the stores of fat existing in their bodies. If now such starved animals be fed on some fat of a different kind from that normally present in their tissues they store up the new form of fat instead of the ordinary kind and it is possible by chemical tests to demonstrate the difference. If then to an animal thus treated, containing abnormal fat in its adipose tissues, a course of phloridzin be given and the fat in the liver resulting from the treatment be analysed, it is found that the fat of this organ consists of the extraneous fat, not of normal canine fat. The clear inference is that the fat found in the liver is not a fatty degeneration in the ordinary sense, in which the fat is derived, or is supposed to be derived, from breaking-down of the substance of the liver cells, but that the fat is brought to the liver by the blood and is merely ingested by the cells from the fluids surrounding them. As a result of Rosenfeld's experiments, which have been adequately confirmed by other observers, considerable doubt is thrown on the commonly accepted views on fatty degeneration. So far no connexion has apparently been drawn between the fatty condition of the liver and the glycosuria, but it seems not impossible that such a connexion does exist. I shall hope to allude to this side of the question later in my third lecture. In any case the condition produced by phloridzin is almost exactly the same as that seen in diabetes, in respect to the condition of the urine, to the acid intoxication, and to the fatty state of the liver; and arguments drawn from its peculiar features may be applied to the human disease.

Nervous system.—The connexion of the nervous system with diabetes has already been alluded to in so far as nervous influences may be effective in determining the onset of the disease. It seems, however, rather the exception than the rule to find any recognisable lesions of this system after death in cases of true diabetes. On the other hand, patients dying from cerebral lesions may exhibit glycosuria up to the time of their deaths. In a certain number of cases classed as diabetes, tumours or other affections of the medulla have been found post mortem. It is at least open to question whether these cases should not rather be described as instances of persistent glycosuria than of diabetes, death being assignable to the cerebral lesion rather than to any nutritional disturbance. Apart from such lesions the changes met with in both brain and spinal cord are most easily explained as secondary changes due to the general wasting and intoxication; such are the atrophy of the convolutions, the widening of the perivascular spaces, the local cysts, the œdema of the membranes, and the dilatation of the ventricles and iter (Dickinson). The localised hæmorrhages sometimes found are analogous to the retinal hæmorrhages characteristic of diabetes and the atrophy and sclerosis of some of the columns of the spinal cord are comparable with the somewhat similar condition which

occurs in pernicious anæmia and are due either to malnutrition or to intoxication. The neuritis which may be met with in the peripheral nerves is also almost certainly due to the general intoxication and is comparable with the neuritis produced by alcohol, a substance very closely allied to sugar, by fermentation of which it is generally produced, but it may equally be due to some secondary intoxication or infection rendered possible by the debilitated state of the tissue. Changes in the sympathetic system are also probably secondary and not causal.

The stomach.—The causation of diabetes was assigned to the stomach by some of the older writers. Thus, Lister placed the defect in this organ and Rollo, who wrote a careful account of the malady, attributed it to excess of gastric fluid, along with some alteration in the quality of the secretion, by which sugar was formed in the organ. There is, however, little or nothing to connect diabetes with gastric disorders so far as morbid anatomy is concerned. It is true that Joneways and Ortel described a case associated with acute gastritis, but this was almost certainly secondary and due to a terminal infection. In most cases the stomach appears to do its work admirably as is proved by the absence of digestive disturbances in spite of the large amounts of food taken. A form of "dyspeptic glycosuria" has, however, been described by Robin in which the sugar appears in the urine only during digestion. The stomach is found dilated and there is hyper-acidity of the gastric juice; the liver may be slightly enlarged. The patients suffer from neurasthenia and there is phosphaturia along with the glycosuria. According to Robin the condition may pass into true diabetes. It seems more natural to connect the condition with the neurotic condition of the sufferers, since diabetes, or at least glycosuria, is not infrequently noticed to accompany neurasthenia, than to suppose any special form of the disease.

The skin.—Apart from the various secondary lesions of the skin due to invasion of pyogenic organisms, such as boils and carbuncles and the local effects of saccharine urine or its decomposition products seen in the neighbourhood of the urethral orifice, there are two conditions of the skin which are said to be specially connected with diabetes mellitus. These are psoriasis and xanthoma. The nature of neither of these is fully understood. Xanthoma appears to be due to a special form of fatty degeneration of the cells of the corium and may, perhaps, be brought into line with the other instances of fatty change already alluded to. Psoriasis has been variously attributed to the presence of an undiscovered organism—as suggested by the ring-shaped lesions of the disease—and to a toxin or dyscrasia. If the former explanation be true—but so far there is no proof of such a cause—its association with

diabetes might be similar to that of the pyogenic affections. If, on the other hand, it is toxic it may be due to the same cause which produces the glycosuria or may be produced by the presence in the skin of sugar or some allied substance. It is noteworthy that among 25 cases of psoriasis Nagelschmidt found eight instances of alimentary glycosuria; whereas among patients suffering from other diseases of the skin who happened to be in hospital at the same time no instance of this condition occurred. Pick, however, denies that alimentary glycosuria is frequently found in patients suffering from psoriasis. The question therefore seems still undecided. It has, however, very little bearing on the nature and manifestations of true diabetes.

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LECTURE II.

Delivered on March 21st.

MR. PRESIDENT AND GENTLEMEN,—In my former lecture I alluded to the relationship of diabetes to changes in some of the organs of the body which I ventured to think were effects rather than causes of the disease. I have to deal to-day with a more important organ in relation to diabetes—*the pancreas*. Attention was first called to the association of pancreatic disease with a case of diabetes by Cowley in 1788. In this instance the pancreas was found to be atrophied and to contain calculi in its ducts. Claude Bernard discovered that removal of the pancreas in animals was followed by a condition similar to diabetes (1855). The first observer, however, who definitely formulated a theory of diabetes as dependent upon disease of the pancreas was Lancereaux (1877). Subsequently (1889) the experimental side of the question was fully worked out in the classical labours of von Mering and Minkowski; their experiments have been often repeated and their results have been fully confirmed, but little has been added to the sum of our knowledge in this field by the work of their successors. The work of von Mering and Minkowski is so well known that it is unnecessary to do more than to allude briefly to the conclusions that may be drawn from it. They proved that total extirpation of the pancreas in dogs and other animals is invariably followed by a condition exactly resembling diabetes—a condition in which there is not only sugar in the urine, dependent upon excess of sugar in the blood, with the ensuing symptoms of increased appetite and thirst, but also an acid intoxication, with the appearance of acetone and diacetic acid in the urine and a tendency to death in coma. Partial extirpation of the pancreas was not followed by this condition, nor was total ablation of the gland if a fragment of it were grafted into some other part of the body; if, however, as usually takes place, this grafted fragment ultimately disappeared, then diabetes ensued as certainly as if the gland had been removed at one operation. Similarly, if the gland be removed in three separate pieces on different occasions diabetes does not occur till the last piece has been taken away. That this effect is not due to the absence of the digestive juice furnished by the pancreas is sufficiently shown by the phenomena which ensue after ligature of the ducts. In most cases no diabetes or glycosuria is observed; in a few instances there is a transient glycosuria with some

increase of appetite and thirst but this passes off within a few days. It was, indeed, objected to these last experiments that the ducts generally re-establish themselves after ligature or section, so that the secretion may once more reach the intestine. To obviate this various experimenters have injected the ducts with substances such as paraffin, soot, and tarry materials (Schiff, Thiroloix, Gley) which produce permanent obliteration of the secretory channels, without causing the appearance of diabetes. Thiroloix, indeed, maintains that by these means it is possible to produce a total atrophy of the pancreas and that yet no diabetes ensues. It is probable, however, that the disappearance of the glandular tissue was not really so complete as he supposed. In some experiments it has been observed that merely separating the pancreas from the duodenum, or handling it, or disturbing it in its relations, may result in the temporary appearance of glycosuria.

It seems to be absolutely proved by these experiments that removal of the pancreas is followed in animals by a condition indistinguishable from diabetes. It is necessary therefore to examine how far clinical and pathological evidence point in the same direction in the case of mankind. Lancereaux in his work on "Diseases of the Liver and Pancreas" described four different conditions of the pancreas which may exist in cases of *diabète maigre* or wasting diabetes—as distinguished from the form of the disease, or rather, in all probability, of simple glycosuria, met with in fat persons. There may be: (1) simple atrophy or aplasia of the gland, in which the cellular elements are diminished in number without any accompanying alteration in the structure of the organ or in the appearance of the cells; (2) atrophy with fibrosis (secondary sclerosis) of the gland and some fatty degeneration of its cells; (3) atrophy with inflammatory fibrosis, the result of infective processes or obliteration of the ducts; and (4) tumours, especially cancer of the head of the pancreas which has led to obstruction of the ducts. This observer, therefore, especially associated *atrophy* of the pancreas with diabetes, though it would seem that he attributed undue importance to disease of the ducts.

Of recent years much attention has been paid to diseases of the pancreas which are now better understood than of old. The chief pathological changes found in it are now recognised to be: atrophy, carcinoma, cystic disease, acute and chronic inflammation, calculi affecting the ducts, and hæmorrhage into its substance and into the surrounding connective tissue. It may also undergo fatty degeneration and may be the seat of abscess-formation and of total necrosis as the result of acute inflammation. It is necessary to consider what evidence there is as to the co-existence of these various diseases with glycosuria and diabetes. The latter is a somewhat rare disease, though not apparently so rare now as in the time of Galen who only saw two cases

of the malady.[1] Still, the total mortality from diabetes is somewhere about 7 per 100,000 of the population (Saundby). Among patients admitted to Charing Cross Hospital I find that diabetics, or those who are so classed, amount to about 6 per 1000 of the whole number of admissions. It has been argued that as diabetes is a rare disease and lesions of the pancreas are also not frequent, the co-existence of the two in any considerable number of cases *ipso facto* renders the causal connexion between them highly probable. But is it certain that pancreatic disease is uncommon? I thought it worth while at the time when I was making post-mortem examinations at Charing Cross Hospital and elsewhere to investigate the question, and with this object I cut sections for microscopical examination of the pancreas from 100 practically consecutive cases. Most of them were from cases on which I myself made necropsies, but some were kindly sent me from Claybury Asylum by Dr. Bolton, by permission of Dr. F. W. Mott, these cases also being consecutive and not in any way selected. Some of my own cases were from the Victoria Hospital for Children and a few from the Samaritan Hospital for Women, at both of which I made necropsies at the time. The series was thus not absolutely consecutive at any one hospital but consisted of unselected cases suitable for examination of the point in question. Their ages ranged from four days up to over 90 years. I had hoped to be able to supplement this very inadequate number from which to draw conclusions by examining the records of necropsies at other hospitals; but I soon came to the conclusion that unless a microscopical examination of the pancreas were made it was impossible to say in any case whether it was normal or not, since in many instances the external appearance of the gland might be unchanged in the presence of considerable alterations in minute anatomy. I therefore felt that statistics of the number of cases in which this organ was healthy or unhealthy could not be safely collected from the records of other hospitals, as it is practically impossible to make microscopical examinations of all organs in every case, and it would not be likely that such examination of the pancreas would be made unless there were some gross alteration in its appearance to cause attention to be directed to it. I have had, therefore, to be contented with my own 100 cases. Among them I found a certain degree of fibrosis present in 15. Of these ten were over 40 years of age, counting among these two whose ages were not actually known, but who appeared to belong to this period of life. It would seem from this that a certain amount of fibrosis of the pancreas is not very uncommon, occurring in some 15 per cent. of patients dying from all causes in hospital, while among persons over 40

[1] This would seem to prove that Galen distinguished diabetes from mere polyuria, of which he could not have failed to observe many instances.

years of age it is much more often met with (ten out of 54) than in those below this age. In 70 cases (not quite consecutive) which I have since examined the proportion in which I found fibrosis of the pancreas present was approximately the same as in the first 100. The youngest patient in the former series in whom I found any increase of fibrous tissue present was aged 29 years and in this case there was a special reason for such a pathological condition in that he was almost certainly a syphilitic subject. That syphilis may be a cause of pancreatic fibrosis is practically certain as a congenital fibrosis of this organ is met with and has been described by Opie. It appears to be a fatal lesion, the infants succumbing within the first few days after birth. No records seem to exist as to the presence of sugar in the urine of such infants. Since the pancreas is thus affected in infancy it is highly probable that in the adult also it, like other organs, will undergo cirrhosis as a result of this disease. Another comparatively young patient in my series who exhibited some fibrosis of the pancreas died from a ruptured aneurysm, which occurrence affords a ground for suspecting the existence in this instance also of a syphilitic taint.

If the results suggested by a small number of figures which I have been able to collect are borne out by further investigation, it would seem likely that a certain amount of fibrosis of the pancreas is a usual accompaniment of advancing age. Possibly it is preceded by some atrophy of the glandular elements, the fibrous tissue merely taking the place of higher cells which have disappeared. The condition may thus be correlated with fibrosis of the arterial system and with chronic granular kidney. Atrophy with secondary fibrosis was assigned by Lancereaux as one of the causes of diabetes. It is interesting to remember in this connexion that diabetes is usually a disease of advanced life so that its incidence somewhat corresponds with that of pancreatic fibrosis. It is clear, however, that some fibrosis of the pancreas may exist without diabetes, for only two cases of that malady came into my series of 100 cases. I did not find any traces of fibrotic change in the pancreas in any of the children whom I had the opportunity of examining; but apart from the congenital syphilitic form of pancreatic fibrosis, an acquired form of fibrosis does seem to exist, as was proved to me by a specimen sent me by Dr. A. D. Jollye of Brixton for examination. This was taken from a child, aged seven years, who had suffered from severe tetany during life. At the necropsy the only visible pathological condition was in the pancreas which was much enlarged. On examining it microscopically I found that it was the seat of marked fibrosis. The cause of this was not ascertainable, though it was impossible not to think of syphilis in view of the irregular distribution of the fibrous tissue. Whether the pancreatic condition had any relation to the tetany was also problematical. This disorder is usually attributed to the

absorption of some toxic material from the stomach and it is possible that an affection of the stomach and duodenum was followed by secondary cirrhosis of the pancreas by extension of inflammation up the duct of Wirsung. Diabetes in children is not common. When it occurs it is rapidly fatal as a rule, suggesting the existence of some extensive or progressive lesion of the pancreas if this organ be at fault.

Opie has distinguished two varieties of fibrosis of the pancreas: (1) one, a coarsely distributed variety, in which the fibrous bands pass between the lobules of the gland, embracing groups of acini in their meshes; this he calls the "interlobular" variety; and (2) a more finely distributed fibrosis in which the new tissue passes between the individual acini ("interacinar" fibrosis). He considers that diabetes is related to the latter (for reasons which I shall mention later), not to the former. The varieties of pancreatic fibrosis are thus somewhat analogous to the types of cirrhosis of the liver, in which we recognise a multilobular or portal cirrhosis, with coarsely distributed bands of fibrous tissue, and a unilobular or biliary cirrhosis in which the fibrous network penetrates between the single lobules. In the latter the liver is often much enlarged, whereas in the former it is generally shrunken if the cases have lasted long. The same appears to be true of the pancreas. The common form of fibrosis is accompanied by shrinking of the gland and often by atrophy or fatty degeneration of the cells. But the organ may, on the other hand, be considerably enlarged. In one case of diabetes, which I had the opportunity of observing before I began to collect a series, the pancreas was of vast dimensions, weighing just one pound instead of some three or three and a half ounces. It was thus more than four times its usual weight and was tough and hard in consistency. Microscopically it was seen to be penetrated by new bundles of fibrous tissue, both coarsely and finely distributed. I shall refer to the details of the case a little later. It may be remarked that the pancreas is an organ in which it is difficult to be certain of the reality of slight degrees of fibrosis, as the connective tissue in it is normally somewhat irregularly distributed.

With regard to the relation of *atrophy* of the pancreas to diabetes Hansemann distinguishes two varieties of atrophy of the gland: (1) one in which there is simple wasting of the cells, and (2) a second in which this wasting is accompanied by fibrosis. The former occurs in cases of general failure of nutrition and is a secondary change; it may be called "cachectic" atrophy. The pancreas is found to exhibit a rounded, almost cylindrical form and to be of normal consistency. It is sharply marked off from surrounding parts and is easily removed from the body, being free from adhesions to neighbouring structures. The cells and lobules are shrunken but the organ is not pigmented, nor is it fibrous. In

the second form of atrophy the pancreas is soft in consistency and dark in colour; it is flattened from before backwards and is closely adherent to surrounding parts. The gland is permeated by an increased amount of fibrous tissue and there may be some cellular infiltration. The condition thus somewhat resembles that of a granular kidney which is fibrous and adherent to the tissues surrounding it and, like granular kidney, it is very probably related to arterio-sclerosis. It is this latter variety of atrophy which is associated with diabetes. In other words, although Hansemann lays stress upon the atrophy it would seem to be fibrosis of the pancreas which is the principal lesion associated with diabetes—a condition apparently analogous to the atrophic form of cirrhosis of the liver. In both organs, however, there seems no means of determining whether the atrophy of the cells leads to increase of fibrous tissue, as in the case of the nervous system, or whether the fibrosis is of an inflammatory nature and contraction of the scar-tissue produces injurious pressure upon the glandular acini.

Fatty degeneration of the pancreas—using the term "degeneration" in a wide sense without determining whether it is an infiltration, so-called, or metamorphosis—is not uncommon. Among my 100 cases I found a recognisable degree of fatty change present in ten instances; in three cases it was combined with some fibrosis. A case of diabetes dying in coma exhibited very advanced fatty change along with fibrous overgrowth, and some degree of fatty degeneration was present in most of the cases of diabetes which I have examined. In fat persons the gland is not infrequently penetrated by columns of fatty connective tissue passing between the lobules, but the cells of the acini appear normal. Hansemann notes that in a few cases of diabetes fatty degeneration of the pancreas has been found after death as the only discoverable lesion.

Calculi in the pancreatic ducts have been associated with a certain proportion of cases of diabetes. Thus, as already mentioned, the original observation of Cowley was of this condition. Hansemann notes that out of 72 cases which he collected from medical literature calculi were the cause found in 14 instances. It is clear that these concretions cannot exert a direct action on the process of sugar-formation, since all that they can do is to block the ducts; and, as has already been mentioned, ligature of these does not seem to be an efficient cause of diabetes or lasting glycosuria. But the continued existence of obstruction to the outflow of secretion is accompanied by injurious pressure in the acini, analogous to the condition present in the kidney in cases of obstruction to the exit of urine. In both organs alike cystic dilatation of the ducts and atrophy of the secreting cells ensue, accompanied by an overgrowth of fibrous tissue. It is to this atrophy of the glandular cells that the diabetes

associated with calculi must be attributed. It has, however, been found experimentally that injection of pancreatic juice into the ducts of the organ is followed by the appearance of sugar in the urine, so that a temporary glycosuria might ensue as the result of impaction of a calculus before any destructive changes occurred in the organ; this glycosuria might pass off if the calculus escaped or was removed, or it might become permanent if no such relief was afforded.

Carcinoma of the pancreas is not a very infrequent condition as a primary lesion. Secondary growths of cancer in this organ do not seem very common. I have met with two cases of secondary deposits of sarcoma in this position; in each case the primary growth was in the thyroid gland, but this was probably a mere coincidence. The relations of carcinoma of the pancreas to glycosuria are somewhat curious. The latter symptom is not constant; it may appear late in the history of the case or it may be noticed early and pass off again. The absence of permanent diabetes in many—indeed, in most—cases of cancer of the pancreas is probably due to the fact that the disease does not destroy the pancreatic cells entirely; in the most extensive cases the new growth rather insinuates itself between the cells so as to obliterate the normal structure of the organ, while in the majority of instances the tumour remains limited to one part of the gland, usually the head, leaving the rest unaltered. The temporary glycosuria observed depends in all likelihood upon interference with the outflow of pancreatic juice which, as has just been mentioned, may produce glycosuria. In many instances of primary cancer there is coexistent fibrosis of the pancreas along with the new growth and it is difficult to ascertain which was the primary condition—whether the cancer produced the fibrosis by obstruction of the ducts of the gland, as a calculus may do, or whether the new growth arose in a fibroid organ, as seems to be the case most frequently in primary cancer of the liver, the tumour originating in all probability in a group of cells isolated by the fibrous overgrowth similar to the groups seen in the so-called multiple adenomata of the cirrhotic liver.

Hæmorrhage into the pancreas may be associated with the appearance of sugar in the urine. The following case may be quoted as an example. A laundress, aged 53 years, was admitted into Charing Cross Hospital under the care of Dr. J. M. Bruce on Jan. 24th, 1893, complaining of abdominal pain, thirst, and dypsnœa. Her previous history had been uneventful; there was no history of syphilis. A week before admission to hospital she was seized with pain in the abdomen which rapidly swelled and became hard to the touch. At the same time she complained of increased thirst and of shortness of breath and had a difficulty in getting about. On examination she appeared to be a well-nourished woman; her face was flushed and her tongue was dry and

covered with brown fur. Her temperature was 100° F. and she complained of great thirst. There was pain all over the abdomen, which was uniformly distended, so that the umbilicus was obliterated. Tenderness was general over the abdomen, but there was increased resistance in the epigastrium and hypochondria, especially on the right side. The bladder was distended and the edge of the liver could be felt about one and a half inches below the costal margin. She was delirious at night, trying to get out of bed continually. She passed from 54 to 60 ounces of urine per diem, the total amount of sugar present varying from 1012 to 1125 grains. Her temperature gradually rose, and on the 29th and 30th she had rigors. On the latter day acetone was noted to be present in the urine. She vomited and became very restless. Finally she died in collapse without any appearance of coma. At the necropsy there was found "a good deal of turbid fluid in the peritoneum; some little lymph between the coils of the intestines." The layers of the mesentery were everywhere separated by a large mass of disintegrated blood clot and blood-stained fluid. The stomach was adherent to the left lobe of the liver and on separating the two several pints of blood-stained grumous fluid escaped. "The fat was everywhere speckled over with opaque dead-white points which appeared to be composed of necrosing fat. ..... In the situation of the pancreas was a breaking-down mass of tissue along with much bloody fluid. Some loose shreds of tissue as big as a fist were floating in this cavity; they appeared to be portions of the pancreas." No other morbid conditions were found.

In this case, therefore, there was destruction of the pancreas by a hæmorrhage, and with the exception of the secondary peritonitis and fat-necrosis this was the only morbid condition. In this patient there had been no symptoms of diabetes before the sudden onset of the illness; yet on her admission to hospital she exhibited all the signs of the malady—thirst, glycosuria, and finally acetonuria. Such a case constitutes a natural experiment on removal of the pancreas in a human being and the results exactly correspond with those obtained in animals. Here, at least, the connexion between a lesion of the pancreas and the onset of diabetes appears to be absolutely proved. The death of the patient was apparently due to the peritonitis accompanying the necrosis of the pancreas and not to the diabetes, as the patient did not die in coma but in a state of collapse. The presence of acetone in the urine in such a case appears to show that no distinction, such as that quoted from Professor Tyson in my first lecture, can be drawn between pancreatic diabetes and "severe diabetes accompanied by acid intoxication." Experiments on animals show that the latter phenomenon is characteristic of pancreatic defect.

If we examine the results of observations as to the coexistence of gross lesions of the pancreas with diabetes

we find very different figures given by different writers. Hansemann, who carefully studied the question and formed the opinion already alluded to that a special form of atrophy with fibrosis was characteristic of the disease, found alterations of the pancreas present in 40 out of 59 cases. Windle found 74 cases of pancreatic disease out of 139 cases; Frerichs, 12 out of 40; Seegen, 17 out of 92; and Naunyn, 1 out of 40 (I quote the figures from Professor Tyson). It seems almost impossible to reconcile the figures given by Naunyn with those found by others. I have not myself had the opportunity of examining many cases of diabetes post mortem since undertaking this inquiry; but of seven cases in which I have examined the pancreas I found distinct alterations present in five, consisting in fibrosis of varying degrees with some fatty change. In a sixth case, that of an old man with advanced arterio-sclerosis and gangrene of the leg, the vessels in the pancreas were markedly sclerosed; the glycosuria had been intermittent. It might be suggested that this was due to intermittent pancreatic failure, analogous to the "intermittent claudication" sometimes met with in arterio-sclerosis. In the remaining case I was unable to discover any noteworthy pathological condition except sclerosis of the vessels. Looking through our post-mortem registers I find in the last ten years 12 necropsies on patients dead from diabetes. In seven of these the pancreas was noted to be small, in four it was distinctly fibrous to the naked eye; in only one case did it appear even macroscopically to be absolutely normal. The microscopical appearances are unfortunately not recorded in the notes.

The difficulty of which I am most conscious in endeavouring to establish a connexion between the pancreas and diabetes is not that of finding pancreatic lesions in cases of diabetes but rather the fact that quite as severe lesions may occur in cases in which there has been no diabetes; for the pancreatic cirrhosis in two at least of my seven cases was only moderately extensive, while I have found very advanced fibrosis apart from diabetes. At the same time diabetes is the condition with which pancreatic disease would appear to be most frequently associated, for whereas five out of seven diabetics[2] exhibited lesions the figures for other diseases are:—

Arterio-sclerosis,	6	cases of	pancreatic	disease	out of	11	cases	examined.[3]
Carcinoma,	4	,,	,,	,,	,,	16	,,	,,
Tuberculosis,	3	,,	,,	,,	,,	14	,,	,,
Aneurysm of the aorta,	1	,,	,,	,,	,,	3	,,	,,
Heart-disease	2	,,	,,	,,	,,	9	,,	,,

[2] If I were to add to these one case of diabetes characterised by almost total replacement of the pancreas by fibrous tissue, from which a portion of the gland was kindly sent me by Dr. Mott, and a second case (referred to below) from which I received a specimen of the pancreas from Dr. R. Salusbury Trevor, my figures would show seven cases of distinct pancreatic lesions out of nine cases of diabetes.

[3] The number of cases of arterio-sclerosis is almost certainly under-

All authorities appear to be agreed that there are a certain number of cases of diabetes mellitus in which no alterations are discoverable in the pancreas. They differ as to the proportion of such cases. On the other hand, many cases exist in which the pancreas is the only organ in the body which exhibits any sign of disease. The attempt to reconcile these facts presents a difficult problem. Several answers may, however, be given. In the first place, the suggestion has been made that it is not the glandular cells lining the acini of the panereas and forming the main bulk of the organ by which the sugar-regulating function is carried on but certain special cells of different formation which are scattered throughout it in small distinct masses. These are the "cell islands" named after Langerhans who first described them. They appear to be formed from the same rudiment as the rest of the pancreas and are epithelial in nature. According to the accepted view they are at first connected with the ducts of the gland and this condition seems to persist for some little time after birth, as Opie has depicted a small duct entering an island of Langerhans in a case of congenital syphilitic pancreatitis. In adult life, apparently, this connexion with the ducts becomes obliterated and the islands remain as small groups of polygonal cells surrounded by a fine capsule which separates them from the surrounding acini. This separation does not appear, however, to be absolute, as it is possible to see islands here and there in which the cells are apparently continuous with the cells of the acini without any intervening fibrous tissue. These groups of cells are richly supplied with blood and are penetrated by a network of capillaries. They are scattered throughout the panereas, but are considerably more numerous towards the tail of the gland. In stained specimens of pancreas the protoplasm of the cells forming these islands seems usually to take on a slightly different colour or a different depth of tint from that of the acinar cells, suggesting a slightly different chemical composition and therefore a different function, but the staining of the glandular cells is not constant and not much weight can be attached to such an observation. The general appearance of the islands of Langerhans thus somewhat resembles that of the glomeruli of the kidney, and they have been called by Kühne and Lea "pancreatic glomeruli." They differ, however, from the renal glomeruli not only in their irregularity of size and shape but also in that they have no connexion with the ducts of the organ, and hence their condition resembles rather that of a ductless gland, such as the thyroid or the suprarenal body, especially in view of their rich vascular supply. It has therefore been suggested that these cells are the source of

stated. I count only those in which this condition was definitely recorded in the post-mortem notes. Moderate degrees of this condition would probably escape record.

the internal secretion of the pancreas. The idea was first mooted by Laguesse in 1895 and was adopted by Schaefer. It has since been supported by Opie and many others who have brought forward cases apparently pointing to a connexion between disease of the islands of Langerhans and diabetes. It may be of interest to mention that attempts have recently been made to connect the hypothetical internal secretion of the testis with certain special cells found in the organ, lying separate from the spermogenic cells of the tubules. If this hypothesis be proved true it will afford some support to the similar suggestion in the case of the pancreas; but the reality of this source of internal secretion is equally far from actual demonstration in the case of both organs.

It has been found that in diseases and injuries to the pancreas the islands of Langerhans often escape while the glandular cells are destroyed. Thus in experimental ligature of the ducts the pancreas appears to be converted into a mass of fibrous tissue, but the islands can often be discovered lying among the new tissue uninjured. This is probably owing to their lack of connexion with the duct-system of the organ; and it is possible to explain in this way the failure to produce diabetes which has been observed after ligature of the ducts or injection of them with tarry materials. Similarly, in some cases of inflammation of the pancreas the islands are said to escape the destruction which affects the acinar cells. In addition to this negative evidence tending to show the persistence of the islands of Langerhans in cases of apparent destruction of the pancreas in which diabetes does not occur, there are brought forward cases in which lesions of these structures have coincided with the existence of diabetes. A peculiar hyaline degeneration of the islands of Langerhans was described by Professor R. Saundby in his Bradshaw Lectures in 1890 and Opie has brought forward cases definitely connecting the condition with diabetes. In his first case, it is true, the degeneration was not confined to the islands but invaded some of the other portions of the gland; but in a later communication he recorded an instance in which this affection was the only visible lesion in a case of diabetes, the islands being apparently picked out by the degeneration and the rest of the pancreas remaining normal. Ssobolew found that in 18 cases of ordinary pancreatic atrophy in which there was no diabetes the islands of Langerhans were quite unaltered, whereas among 15 cases of diabetes there was recognisable alteration in these structures in 13 instances. Opie points out that in cases of coarse fibrosis of the pancreas the islands are not generally affected, whereas in the fine variety of fibrosis of the gland the new tissue tends to invade the islands and so to cause diabetes. Schmidt has seen a case of diabetes in which there was acute inflammation of the islands of Langerhans, with only a few similar foci in the rest of the pancreas; he

points out, however, that in this case—a child, aged ten years, who was passing 6·8 per cent. of sugar in the urine—the diabetes must have lasted longer than the inflammation of the islands. Yet it is difficult to imagine a cause of inflammation which could pick out these structures and spare the rest of the pancreas. Seeing that the islands are shut off from the ducts of the gland no irritant could reach them from this source ; it is only through the blood-vessels or lymphatics that it could be brought to them, and these equally supply the rest of the organ. It seems, therefore, permissible to question whether there was not in this case a preceding lesion of the islands which rendered them susceptible to some irritant which was not capable of harming the glandular cells or whether the existence of degeneration in these structures may have given rise to irritating products which caused accumulation of inflammatory cells within their capsules. Schmidt quotes two cases of diabetes associated with pancreatic calculi in which the islands appeared normal. In eight cases out of 23 of diabetes he could find no pathological change at all in the pancreas. Weichselbaum and Stangl describe four possible conditions of the islands which may be met with in diabetes: (1) diminution in size or number ; (2) vacuolisation ; (3) atrophy ; and (4) induration or hyaline degeneration. They found affections of the islands present in every one of their cases of diabetes. Gutmann out of 14 cases of diabetes found changes in the islands in four ; in six there was atrophy of the pancreas as a whole, similar to that described by Hansemann ; in two cases no changes at all could be discovered. In three of my seven cases of diabetes the islands of Langerhans appeared to be greatly reduced in number. It seems possible that they undergo fatty degeneration and so disappear, as the distribution of the fatty patches found in such pancreases corresponds somewhat with that of the islands in normal glands. In three of my cases they appeared quite normal. In the arterio-sclerotic case previously mentioned they appeared to be atrophic, the islands themselves being vacuolated owing to disappearance of many of the cells.

The most remarkable statistics on disease of these structures in diabetes are those given by Lancereaux, who states that out of 167 collected cases no less than 130 showed alterations in the islands. Such results are very striking and if confirmed by others will go far to prove the connexion between these structures and diabetes. Experiment upon the islands alone is almost impossible. Lewaschew stated that by carbohydrate feeding and the injection of pilocarpine many of the acini of the pancreas may be converted into islands, but Opie repeated the experiments and was unable to confirm these results. Herter and Richards state that injection of suprarenal extract causes granular degeneration of the cells of the islands. It has been suggested that the islands are immature acini waiting to be converted into

mature glandular cells, but there appears to be no increase in the islands in a fragment of the pancreas left behind when the rest is removed, so that they do not seem capable of giving rise to new acini. On the other hand, Schmidt states that in some cases of fibrosis the islands are increased in number and size and he believes that they may be formed out of secretory tissue. He speaks of cases in which whole lobes of the pancreas are converted into cells resembling those of the islands. I have myself noticed that in many instances a curious change is found in large areas of the gland, the cells being no longer arranged in acini around central spaces but lying apparently closely packed side by side without any definite structural arrangement. As to what the nature of the change may be I have no suggestion to make, as the condition was met with in cases in which other parts of the gland seemed quite normal, while the cells in the altered portions stained in a manner similar to healthy cells. There does not seem, however, sufficient evidence upon which to consider these altered portions of the pancreas to be converted into a new formation of "islands" and it seems probable that the condition is a post-mortem change. I have, however, seen portions of pancreas in which the islands were so numerous as to form a large proportion of the tissue present. With the view of Schmidt that the islands are formed from the glandular acini I am inclined to agree, in view of the appearances presented in many cases. Not only are the islands quite irregular in shape and size but one sees islands in which the typical cells are surrounded by a ring of secreting cells; others, again, in which masses of these latter are inclosed within the insular cells, and others in which cells staining like ordinary glandular elements appear to form part of the island and to merge into its structure. Increase of the islands has been described in some cases of infective disease, but the number and size of these bodies vary so greatly in different specimens of pancreas without any ascertainable cause and also in different parts of the same pancreas that it is practically impossible to fix upon an average number or size which is to be considered normal and which shall serve as a standard of comparison.

Ssobolew found in one case of diabetes enormous enlargement of the islands ("struma of the islands"), so that some of them measured as much as 1·5 millimetres in diameter. He suggests that this represented either a compensatory hypertrophy to make up for the loss of others which had disappeared or a process of tumour-formation. Hyaline degeneration was present in some of the islands in this case, apparently starting in the capillaries, not in the cells themselves. The nature of the degeneration would thus seem very similar to that of amyloid change which starts in the vessels and only injures the cells secondarily by pressure. In a specimen kindly given me by Dr. Salusbury Trevor, of St. George's Hospital, the hyaline portion of the

islands also seemed in most cases to be formed of degenerated capillaries, but here and there hyaline areas seemed to be formed of degenerated cells. Hence it seems doubtful whether there are not several conditions included in this so-called hyaline degeneration. On the whole, it is impossible at present to say that the relation between the islands of Langerhans and diabetes has been established. Hansemann, who has made a careful study of the pancreas in diabetes, denies that there is any connexion. Opie's case does, indeed, at first sight appear to afford an *experimentum crucis*, but it is so far lacking in sufficient corroborative evidence to establish a general rule. I could not be certain of any special alteration of these structures in any of my cases—certainly quite as marked changes were present in non-diabetic subjects. On the other hand, Lancereaux's statistics are very striking. Further, it seems to be admitted that hyaline degeneration of the islands has scarcely ever been observed in any other disease than diabetes,[4] so that there appears to be some connexion between them. The possibility is not, however, excluded that in diabetes the degeneration of the islands may be a secondary phenomenon. Still, the suggestion of these structures as the source of the internal secretion of the pancreas is a tempting hypothesis and explains some facts hitherto difficult to understand. More investigation is necessary before the question can be regarded as settled.

Even granting the connexion of the islands of Langerhans rather than of the secretory cells of the pancreas with diabetes there remain some cases to be explained in which no alteration of any part of the pancreas can be discovered. With regard to these we have to remember that, as has already been mentioned, we are dependent for our diagnosis of diabetes upon one symptom alone—the presence of sugar in the urine—and it is evident that such a criterion is liable to be fallacious. It can hardly be doubted that we at present include under the term diabetes cases of very different natures. Every clinician must be familiar with cases in which sugar is found in the urine of a patient who comes for treatment for some entirely different condition—cases in which the patient appears to suffer no inconvenience from his glycosuria and goes about his work as usual until diabetes is diagnosed on account of the

[4] I have found hyaline degeneration present in one case apart from diabetes, the patient being a woman, aged 63 years, who died after an operation for gall-stones. There was extensive arterio-sclerosis of the pancreatic vessels and here and there patches of necrosis of the glandular cells. In one or two islands hæmorrhages had occurred. It seems not impossible that the hyaline change may be a result of arterio-selerosis; its possible association with capillary hæmorrhages may be worth investigation. I have seen what I believe to be early stages of hyaline degeneration of the islands in other cases, but it is difficult to be certain of this. The existence of some degree of hæmorrhagic extravasation into the islands is not very uncommon. I have found it present in five cases out of the last 70, in which I paid special attention to these structures.

discovery of sugar. It seems almost certain that many of these persons are the subjects of an entirely distinct condition from those acute cases in which thirst, increased appetite, and rapid wasting are such distressing features. It is with the latter type of case—*diabète maigre*—that Lancereaux would associate pancreatic affections. They seem, indeed, to constitute a class by themselves, worthy of recognition as a separate disease, to which we should limit the name of diabetes, classifying the others as various forms of glycosuria, in which the appearance of sugar in the urine is indeed often a prominent feature, but in which there does not exist that internal breaking down of the tissues into sugar characteristic of the graver disease.

But a second possible explanation has to be considered and that is the fact that we are not yet in a position to exclude the existence of disease in any organ because our present methods of examination do not reveal definite structural alteration. Although true functional disease as opposed to organic cannot exist, yet there are only too many conditions in which the perversion of function is all that we are able to recognise. Minute alterations in the molecular composition of the pancreas may be present in some instances which we cannot discover with the microscope.

Thirdly, we have to take into consideration the influence of the nervous supply of the pancreas. It is conceivable that although the cells themselves may be normal in structure, yet if they be acted upon by abnormal nervous stimulus they will give rise to different products or fail to produce any secretion at all. Of the effect of nervous influence upon the origin and extent of glycosuria we have many proofs. In many cases probably these nervous stimuli act upon the liver in a manner analogous to the diabetic puncture, thus causing the outpouring of increased sugar into the blood. But in some in which true diabetes ensues it may be that the internal secretion of the pancreas is affected. If there can occur, as is well known, a sudden drying up of the salivary secretion as a result of fright we can equally suppose a sudden cessation of the formation of an internal secretion. If a total alopecia may result from shock and persist subsequently—and cases of such an occurrence have been met with—the defect of pancreatic secretion may equally persist as a permanent lesion.

In connexion with the question of the relation of pancreatic disease to diabetes it may be of interest to consider how far the known causes of the former correspond with those responsible for the latter condition. I have already alluded to the fact that both diseases tend to occur towards the latter part of life, diabetes being usually first complained of after 40 years of age and pancreatic fibrosis also occurring with greater frequency after this period. The connexion of arterio-sclerosis with fibrosis of the pancreas is also recognised, and this degenerative state has been frequently noted in diabetics, in whom it is

probably responsible for most of the cases of gangrene of the extremities which occur, as well as being one of the assigned causes of the onset of the disease. The association of gout with diabetes is not improbably due to this accompaniment of both conditions. Another cause of pancreatic fibrosis, as already pointed out, is syphilis, and this infection almost certainly plays an important part in the production of a certain proportion of cases of diabetes; in my series, as previously stated, it was a likely factor in 12½ per cent. The most important cause of pancreatic fibrosis is probably the entry of micro-organisms by the ducts from the duodenum. This has been proved experimentally to cause inflammation of the gland and subsequent scarring. A history of digestive disturbance is not uncommon in diabetic cases and a certain number seem to date from a definite attack of vomiting and diarrhœa. Such instances may perhaps be associated with pancreatitis from intestinal catarrh. It might also be suggested that the abdominal, and specially epigastric pain, to which I have alluded as so often complained of by these patients, may be connected with inflammation of the pancreas. The apparently infective cases of diabetes, such as those collected by Hutinet, may perhaps be attributed to this method of causation, although this observer suggests that the infective agent in such instances acts by producing a condition of arterio-sclerosis.

Finally, the frequency of a history of alcoholism in diabetic cases fits in well with the pancreatic hypothesis of its causation. As cirrhosis of the liver is caused by this drug so fibrosis of the pancreas is almost certainly due in many instances to its action. Apart, then, from hereditary influences—and some "family" cases are attributed by Hutinet to infection—there is a considerable degree of correspondence between the causes of acquired diabetes, if it may so be called, and those of pancreatic affections.

In view of the difficulty which at present exists in explaining all cases of diabetes on the basis of pancreatic defect various suggestions have been made in the direction of a joint action of this organ with some other in the regulation of sugar metabolism. In looking round for some organ to which to assign the complementary rôle attention naturally fell first upon the liver. As indicating a connexion between the two it is pointed out that removal of the pancreas causes disappearance, or, at all events, diminution, of the glycogen in the liver, only traces being left a few days after the operation, even when the animals receive a rich carbohydrate diet. On the other hand, injection of pancreatic extract into animals has an exactly similar effect, the diminution in the glycogen being proportional to the amount of material injected (Tyson). Again, if blood is caused to pass through the liver it is found that a certain proportion of the glycogen contained in the latter is removed in the process. If, however, the blood is first caused to pass through the pancreas less sugar is

extracted in its subsequent journey through the liver (Lépine). On the other hand, Hirsch found that an emulsion of hepatic tissue destroyed more sugar if an extract of pancreas was added to it. These results appear contradictory and at present inexplicable. Ohlmacher states that the islands of Langerhans show hypertrophy in cases of hepatic disease and regards this as a compensatory hypertrophy to make up for hepatic defect. An elaborate hypothesis as to the interaction of the liver and pancreas in the process of sugar-regulation was formulated by Chauveau and Kauffmann. According to these authors there exists in the medulla a special centre which restrains the formation of sugar in the body and this centre is stimulated by the pancreas. On the other hand, there is a centre in the cervical cord which stimulates the formation of sugar and the pancreas depresses the activity of this latter. These centres together regulate the sugar-forming process which is actually effected by the liver. This hypothesis cannot be said to have proved fruitful or helpful in investigating the problems of diabetes.

In connexion with the question of a possible interaction between the liver and the pancreas allusion may be made to the curious condition known as hæmochromatosis or bronzed diabetes. This affection was first described by Hanot and Chauffard in 1862 and since then a fair number of cases have been recorded, though it remains a very rare disease. The following case which I had the opportunity of observing was apparently an instance of this affection. A man, aged 60 years, was admitted to Charing Cross Hospital under the care of Dr. Bruce, on June 7th, 1898, complaining of severe pain across the abdomen. He was almost certainly of alcoholic habits but denied that he had suffered from any serious illness in his previous life. He had been losing weight for about a year previously to admission. For the last fortnight he had suffered from loss of appetite and a feeling of depression and he had noticed some swelling of his legs and scrotum. Finally, he had been seized with excruciating abdominal pain, of sudden onset, which had "doubled him up" and caused him to come to the hospital. When seen he was still in great pain and was sweating profusely. He was slightly jaundiced. His abdomen was full and there was tenderness over the right hypochondriac region. The liver was felt to be enlarged. His temperature on admission was 102° F. It fell in the course of the next few days and the pain diminished, but the general condition remained the same for some time. On June 14th sugar was noticed to be present in his urine and by the 20th it had reached a large amount. Then it diminished and on the 22nd and 23rd was entirely absent. On the 24th there was 8 per cent. present and on the 25th there was none at all. Subsequently the sugar reappeared and remained constantly present till his death. He improved greatly in his general condition for the

first four weeks of his stay in hospital and was on the point of being discharged (July 5th) relieved when he developed erysipelas of the face which proved fatal on July 13th. At the necropsy the pancreas was found to be of the enormous size already recorded (weighing one pound); the liver was greatly enlarged, weighing four pounds two ounces, and was the seat of a finely-distributed cirrhosis. There was a considerable deposit of dark pigment in the fibrous tissue of the organ and in the peripheral zone of the lobules. There was no other discoverable disease nor were other organs visibly pigmented. The pancreas was free from pigment.

The three classical features of hæmochromatosis are glycosuria, hypertrophic cirrhosis of the liver, and pigmentation of the skin and internal organs. Of the viscera the liver presents the greatest degree of pigmentation, but the cells of the pancreas and of the salivary glands and those lining their ducts are also affected; and according to Rabé the lungs are also the seat of pigmentation. The pigment is supposed to arise by a breaking-up of the blood-corpuscles and the pigmentation of the organs takes place in the process of eliminating the products of the broken-down hæmoglobin. Two separate pigments have been isolated, a brown substance containing iron, said by Auscher and Lapicque to be a hydrate of iron; and a black one free from iron. Neither cirrhosis of the liver nor glycosuria is, apparently, invariably present in this disease, nor is a condition of fibrosis of the pancreas always found. The relation of the condition to glycosuria presents, therefore, a very interesting problem. Since glycæmia (as evidenced by glycosuria) is not invariably present it cannot be, as suggested by Hanot and Chauffard, that the existence of sugar in the blood is the cause of the breaking up of the blood corpuscles—an idea improbable in itself, since in most grave cases of diabetes, in which there is a large quantity of sugar in the blood, there is no evidence of pigmentation. The glycosuria of bronzed diabetes seems, indeed, to be a late occurrence in many cases. The peculiar condition of intermittent glycosuria which was found in the case above recorded has not, so far as I know, been previously noticed in association with this condition; but it seems that the disease is susceptible of cure, as in a case recorded by Murri; in this, curiously enough, there were no signs of cirrhosis of the liver; the pigmentation of the skin and the glycosuria disappeared under treatment. It is tempting to suggest that the presence of sugar in the urine in those cases—at all events, in the early stages—is due to disturbance of the liver and is a glycosuria not a diabetes. More probably, perhaps, we are in the presence of a functional disturbance of the pancreas. In some cases, as in the one which I have recorded, the pancreas undergoes serious organic changes towards the end of the illness; and if the affection of this organ is sufficiently grave, true diabetes ensues. The cells of the pancreas did not appear to have suffered any structural

change from the fibrosis in Dr. Bruce's case; this may, perhaps, account for the glycosuria being intermittent and not continuous, but it might be anticipated that if the fibrous tissue subsequently contracted or the cirrhosis became more pronounced, permanent interference with the functions of the organ would ensue and lasting diabetes—if this be really connected with pancreatic insufficiency—follow. What may be the source of the poison which causes the destruction of the blood-corpuscles there are apparently no data to help us to determine. The existence of a biliary cirrhosis of the liver and the pigmentation of the abdominal organs to a greater degree than those elsewhere seem to point to a source in the alimentary canal, and the cirrhosis of the pancreas would seem to confirm this conjecture, since, as has been previously mentioned, infection passing along its duct appears to be the usual cause of fibrosis of this gland.

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LECTURE III.

Delivered on March 23rd.

MR. PRESIDENT AND GENTLEMEN,—In my first lecture I ventured to suggest that the essential nature of diabetes mellitus, as opposed to mere symptomatic glycosuria, consisted in an internal formation of sugar from the tissues of the body, while the liver had nothing to do with this condition, being responsible only for a possible aggravation of the existing symptoms by temporary increase of the sugar existing in the blood and thence appearing in the urine. In my second lecture I pointed out some of the reasons which exist for believing that defect in the pancreas is responsible for diabetes. I also mentioned that suggestions had been made with regard to a possible interaction between the pancreas and other organs in the process of regulating the formation and destruction of sugar and dealt with the question of the alleged action of the liver in this respect. Two other organs must also be alluded to as suggested partners with the pancreas—the suprarenal body and the thyroid gland.

The suprarenal body.—The hypothesis of a joint action of this gland with the pancreas is supported by definite experimental evidence and a special form of diabetes, the *Nebennierendiabetes* of the Germans, has been supposed to exist. Experiments show that the injection of suprarenal extract is followed by the appearance of sugar in the urine and the condition is seemingly very similar to true diabetes. The sugar may appear in the urine even when the animal receives only a proteid diet. Feeding by the mouth with suprarenal extract does not produce glycosuria, and subcutaneous injection of it is less efficacious than intraperitoneal. Croftan has called attention to the pigmentation of the skin which occurs in hæmochromatosis as well as in Addison's disease, and has used this resemblance as an argument in favour of a connexion between the suprarenal body and diabetes. Since, however, glycosuria does not usually occur in Addison's disease it is clear that it is not defect in the function of the suprarenals which leads to glycosuria, whereas it is with such defect that pigmentation seems to be connected; hence the argument does not seem valid. On the other hand, an excessive action of the suprarenal might conceivably be responsible for diabetes as experiments suggest. The secretion of these glands when artificially injected appears to act upon the pancreas and to

induce glycosuria secondarily. Thus, it is found that painting the extract upon the pancreas is followed by an excretion of sugar, whereas similar application to the liver or spleen is not productive of the same result. Curiously enough, the surface of the pancreas when thus treated is stated to become pink and hyperæmic instead of blanched, as is the case with other parts which are similarly treated. The property of inducing glycosuria when applied to the pancreas is not, however, confined to suprarenal extract but is exhibited by other reducing agents, such as sulphurous acid, ammonium sulphide, coal-gas, carbonic oxide, &c., so that it is to the reducing action of the suprarenal secretion and not to any specific effect that the appearance of the glycosuria is to be attributed. It is, indeed, said that in fatal cases of poisoning by an overdose of suprarenal extract the cells of the islands of Langerhans are the seat of granular degeneration, while the other cells of the pancreas are not equally affected, but this statement needs confirmation. In any case, the peculiar effect of the secretion of the suprarenal body in producing glycosuria must be attributed to its action on the internal secretion of the pancreas, and there is no evidence that in spontaneous disease any overaction of these bodies takes place or that they are in any way connected with the origin of diabetes mellitus.

The last organ which has been supposed to exert a joint action with the pancreas in destruction of sugar is the *thyroid gland*. Its claims have been urged recently by Lorand of Carlsbad in a lengthy monograph on the production of diabetes. This writer states that in diabetic patients the thyroid is often markedly enlarged—a condition which is not, so far as I know, generally noted in text-books as a symptom of the disease and which I have not personally observed in these cases. He further points to the frequent presence of sugar in the urine of patients suffering from Graves's disease; to the onset of this condition as a result of fright or mental stress—factors which may act as causes of diabetes; and to the sweating which some diabetics exhibit, resembling the sweats so common in Graves's disease, which also may be accompanied by pruritus, pigmentation of the skin, and psychical phenomena. All the symptoms of diabetes can be induced, according to Lorand, by administration of excess of thyroid extract. He considers that the thyroid, the pituitary body, the suprarenal bodies, and possibly the testes and ovaries are all vascular glands (*Blutgefässdrüsen*) and that the islands of Langerhans in the pancreas are also to be placed in this class. All these structures are correlated in function, and defect of one of them produces alterations in the others. Thus in cases of Addison's disease the pancreas is often, he affirms, large and hyperæmic, while the thyroid is small and atrophic. He thus brings myxœdema and Graves's disease, acromegaly,

Addison's disease, and diabetes into one group of disorders depending upon alterations in the vascular glands—a sufficiently heterogeneous collection, though perhaps hardly equal to that embracing gout and rheumatism, epilepsy, Raynaud's disease, megrim, hysteria, Bright's disease, chlorosis, and diabetes itself, seriously maintained by one of the Fellows of this College to be all due to poisoning with uric acid introduced with the food (Haig). Lorand states that it is chiefly in female diabetics that actual enlargement of the thyroid is present; though why the other sex should not also exhibit the same alteration is not clear. He further says that post mortem the gland is soft and that the amount of colloid substance present in it is increased. He quotes some other writers who have found changes in the gland; thus, Rosenfeld noted them in three cases out of 15, while Bachstein and von Noorden record the existence of enlargement in different proportions of their cases. Some support, perhaps, is lent to Lorand's views by the experiments of Knopfelmacher, who examined the alimentary capacity in regard to assimilation of sugar in two patients suffering from congenital myxœdema; he found that the assimilative power for sugar was much greater in these cases than in normal persons. Lorand also claims to have obtained good results in the treatment of diabetes by the use of milk derived from animals which had undergone thyroidectomy. It would thus seem that the presence of sugar in the urine may in some cases be connected with an over-activity of the thyroid gland. There does not seem to be sufficient evidence that this organ is at fault in true diabetes. In a case which I recently examined the thyroid gland appeared quite normal both in size and structure. I also remember reading an account of a case in which diabetes coexisted with myxœdema though I cannot put my hand upon the reference. It is, however, desirable to pay careful attention to the condition of these vascular glands in necropsies upon diabetic cases in order to ascertain the frequency with which pathological changes occur in these parts.

Pathogeny.

I have now to consider some of the views which have been held as to the pathogeny of the disease—the actual mode of production of the defect in metabolism which constitutes diabetes—and to bring before you any facts which appear capable of throwing light upon the difficult problems involved. In the first place, if we ask in what way the pancreas exercises an influence upon the production or assimilation of sugar, it must be confessed that its mode of action is not by any means clear. Two alternatives were originally suggested by von Mering and Minkowski: (1) that the pancreas forms an internal secretion necessary for the regulation of the sugar-forming and destroying

activities of the organism; and (2) that it may neutralise some poisonous material formed elsewhere, which acts injuriously upon these processes. The authors just named discarded the latter theory and adhered to the former. The pancreas would thus come into the same category as the thyroid gland, the existence of an internal secretion from which is now definitely established, and with the ovaries, testes, suprarenal bodies, pituitary body, and thymus in the case of which an internal secretion remains hypothetical, possessing varying degrees of probability in the cases of the different organs mentioned. It may be remarked that it is not the fact of the existence of an internal secretion in these cases which is questionable, for every organ and tissue in the body must in one sense form an internal secretion, inasmuch as it casts off into the circulation substances formed in its life processes—waste products in fact. The question is as to the usefulness of the materials thus formed to other parts of the body. In the case of the thyroid the useful character of its secretion has been most conclusively demonstrated by the results of feeding myxœdematous patients with the substance of the gland. Unfortunately this proof does not exist in the case of any of the other glands in question—possibly because the digestive juices destroy the substances manufactured by them. In the case of the pancreas an instance is, indeed, reported by Wegele in which the use of pancreatic extract caused cessation of glycosuria in a case of apparent diabetes with fatty stools. It is interesting to note that in this instance alimentary glycosuria remained after the treatment, a fact which may afford some support to the view which I have suggested that alimentary glycosuria and diabetes are in many cases quite independent processes. It is held by most authorities that in cases of mere alimentary glycosuria no alteration can be made out in the pancreas (Wille).

Now, in endeavouring to elucidate the possible action of the pancreas upon metabolic processes it is natural to seek to associate it with views recently set forth as a result of study in quite a different field of pathology—namely, that of infection and immunity. The whole subject of immunity was exhaustively discussed two years ago by Grünbaum in his Goulstonian lectures and I need not do more than allude to the salient points which bear upon my present subject. In the first place it is found that when bacteria enter the circulation, or when blood corpuscles from one species of animal are injected into one of another species, these intruders are destroyed by the interaction of two distinct bodies, one of which—the alexine or complement—exists naturally in the serum of normal animals, while the other—the copula or immune body—is formed in response to the stimulus of the injected foreign material. The use of the second body seems to be to unite the alexine to the intruding bacterium or corpuscle and thus enable it to destroy the latter.

We are here introduced to chemical actions of great complexity in which three or more bodies take part, as contrasted with the simpler reactions of non-vital chemistry in which two bodies are generally concerned. We may compare with the processes sketched above that of the coagulation of the blood, in which it has long been known that three or more substances take part—the fibrinogen, the fibrin-ferment and calcium salts; or the action of the digestive ferments, pepsin and trypsin, in the presence of acids and alkalies respectively; or the curious interaction between pancreatic secretion and intestinal juice, in which the inert protrypsin is rendered active by enterokinase. One is tempted to speculate whether we may here be in the presence of a general law of vital chemistry, by which a complicated reaction between three or more bodies—one of which is generally a ferment—is substituted for the simpler interchanges in non-living materials.

Further, in studying the formation of antitoxins Professor Ehrlich was led to formulate his well-known hypothesis of side-chains or receptors. According to this living cells consist of a central mass of protoplasm to which are attached outlying groups of molecules (side-chains or receptors) having the property of entering into combination with bacterial toxins. Now, since it would obviously be better for an organism to possess no receptors capable of uniting with toxic molecules we cannot suppose that the side-chains exist for the purpose of combining with these. It is therefore held that they are primarily intended for the assimilation of food molecules and are only accidentally capable of uniting with toxins. It thus seems possible that the assimilation of sugar by the tissues is carried on by some process allied to the union with toxins. The phenomena of diabetes may thus some day be brought into line with these observations in one of several ways.

1. In the first place, a view very commonly held is that the disease consists in a defective power of assimilating sugar, the defect residing in the tissues throughout the body. It would appear at first sight tempting to suppose that the connexion of the pancreas with diabetes lay in the formation by it of some copula by which molecules of sugar are anchored to the cells; if this be not supplied the assimilation of sugar will then be no longer possible. An analogous defect might be supposed to exist in myxœdema, the thyroid gland here failing to supply an intermediary substance necessary for the utilisation of some other form of cellular pabulum. I do not, however, think that this is the true explanation for more than one reason. In the first place there does not seem to be any convincing evidence that such failure in the assimilation of sugar by the tissues actually exists. The presence of fat-droplets in the muscles and elsewhere may indeed be pointed to as evidence of lack of normal assimilative powers but it can be otherwise explained. Secondly, as

I previously suggested, it seems certain that in the terminal stages of diabetes sugar is formed from the tissue cells and it seems preferable to apply this explanation of the excess of sugar present in the blood to the whole course of the disease. Defect in the formation of an intermediary body would not explain this phenomenon.

2. We may, however, consider in this connexion the hypothesis advanced by Lépine, who explains the phenomena of diabetes by the absence from the blood of a sugar-splitting ferment which it normally contains. He finds that healthy blood possesses the power of causing the disappearance of a certain amount of the contained sugar when it is allowed to stand. Diabetic blood, on the other hand, possesses this property to a notably less degree according to this observer. Croftan has supported Lépine's observations of a power of destroying sugar resident in the blood and lymph. He states that the glycolytic power of the blood is diminished after removal of the pancreas. He also claims to have isolated the ferment by which this action is performed and to have identified it with trypsin. He finds that in the presence of hæmoglobin trypsin has the power of destroying sugar, but apart from the former the normal pancreatic juice has not this property. The glycolytic ferment of these writers would be analogous presumably to an alexine rather than to a copula. Croftan considers that it is formed by the pancreas. Other observers have, however, pointed out that the glycolytic power of the blood increases after it has coagulated, thus appearing to be a non-vital phenomenon, while the process depends to a considerable extent upon the amount of water present in the blood (Biernacki), so that the failure of diabetic blood to destroy sugar may be dependent upon its concentration. Umber found that the glycolytic power of the blood was not increased in the pancreatic vein, as it would have been had the pancreas formed the destructive body. With regard to the glycolytic power of the tissues Giacco found that it varied in different organs, being great in the heart and little in the pancreas. He also found that it remained after boiling the tissue and so was not a vital action. It is interesting to note, in view of the acid poisoning which exists in diabetes, that according to this observer alkalies increase the glycolytic property while acids diminish it

3. If the action of the pancreas, then, is not in the direction of assisting in the utilisation of sugar, there remains the suggestion that it in some way neutralises or destroys a poison which either interferes with some part of the process by which sugar is assimilated or increases the formation of sugar within the body. This the pancreas might do by absorbing the poison and using it for its own metabolic processes, or by forming an antitoxin which would meet and neutralise the toxin in the blood. In the

latter case we should again be in presence of a phenomenon analogous to those supposed to occur in bacteriolysis and immunity. Once more it must be confessed that the evidence in favour of a toxic origin for diabetes is hopelessly scanty; yet there are a few indications pointing that way, and in the state of darkness which prevails as to the pathology of this disease the smallest ray of light is better than none. In the first place we have the undoubted fact that experimentally certain poisons are capable of producing a condition closely resembling diabetes—indeed, as far as we can see, identical with it. The most notable instance—that of phloridzin poisoning—has already been referred to, but other substances, such as diuretin and uranium nitrate, may also produce at least glycosuria, while the effect of suprarenal extract and other reducing substances applied to the pancreas has just been mentioned.

With regard to the actual presence of poisons in diabetes very little direct evidence has been brought forward. Klemperer was apparently the first to suggest that there was present in the disease a poison which interferes with the oxidation of sugar. This hypothesis has been revived by Leo. Long ago Minkowski made experiments to investigate the matter by injecting the blood of a dog rendered diabetic by removal of the pancreas into a normal dog, but the result was negative and indeed was so almost of necessity, since even if the blood of the diabetic dog contained a poison which ought to have been neutralised by its pancreas, yet the normal dog possessed a pancreas capable of dealing with the poison. Lépine injected guinea-pigs with a watery solution of the blood of a diabetic dog and produced a glycosuria lasting for some days, whereas a similar experiment with the blood of a normal dog produced only a very transitory appearance of sugar. From this he concluded that the diabetic organism contains special leucomaines or toxins of internal manufacture. On the other hand, injections of blood derived from pneumonic patients seemed to have a similar power of inducing glycosuria, so that the value of the experiment does not seem very high. Further, the injection of pancreatic emulsion or extract does not seem to influence the condition of animals who have suffered experimental pancreatectomy. The attempt to associate diabetes with an infective micro-organism has—one might say, of course—been made. Topfer and Freund injected animals with the contents of the intestines of diabetic patients and thereby produced a lasting glycosuria; and Hammerschlag and Kauffmann obtained bacteria from the intestines of diabetics and produced a similar result by feeding experiments and by intravenous injections of the organisms. These experiments are not very convincing. It is easy to set up glycosuria in animals in many different ways and there does not seem to be evidence in any of the

experiments that a condition analogous to diabetes mellitus was produced. As previously mentioned, there is little evidence that in man diabetes is an infectious malady; even Hutinet, who maintains the possibility of infection, believes that diabetes is a secondary result dependent upon the production of arterio-sclerosis.

On the whole, then, while there is reason to suspect that diabetes may be due to the action of some toxic substance formed within the body, which is normally neutralised or destroyed by the pancreas, nothing approaching to proof of such a substance or such a condition has so far been established.

Acid intoxication.—There remain to be considered one or two sides of the question of diabetes which may throw light upon the nature of the process. The first of these is the so-called acid intoxication which forms so characteristic a feature of the graver cases of the malady. In this condition the alkalinity of the blood is diminished owing to the formation in the system of acid substances which combine with the alkali present in the body fluids. Coincidently, and apparently as a result of the increase of organic acids present, there is given off some excess of ammonia which combines with these and is excreted in this combination in the urine. An increased amount of ammonia in the urine is thus characteristic of acid intoxication. The acids formed appear to be chiefly oxybutyric, amido-butyric, aceto-acetic, and others perhaps belonging to the same series, which is intimately connected with the volatile substance, acetone, which gives the sweet smell to the breath of diabetic patients. Acetone is said to occur normally in the urine in minute quantities, too small to be recognised by ordinary clinical tests; but in diabetes it is much increased, and almost as much may be eliminated by the lungs as by the urine. It is accompanied in the latter fluid by aceto-acetic acid which gives the characteristic red colour with perchloride of iron. Acid intoxication may occur in other conditions besides diabetes, though it is most profound in this disease. Thus a certain degree is seen in the summer diarrhœa of children, in starvation, and in many fevers. Acetone is also increased in the urine after the administration of ether and chloroform. In all of these conditions, however, it seems to be a feature of no clinical importance; in diabetes it is of very grave urgency, being the forerunner of the fatal coma which terminates so many cases.

An alkaline reaction appears absolutely necessary for the existence of vital activities in the tissues and grave disturbances of nutrition soon occur if an animal is caused to lose alkali which cannot be replaced from the food. Bunge considered that the toxic substance which accumulates in the body in such cases of withdrawal of alkalies is sulphuric acid. The condition would thus be equivalent to sulphuric acid

poisoning. If acids in excess are administered to animals respiration increases in frequency and the pulse-rate rises. Finally, ataxy and convulsions occur and the animal dies in coma. It seems that carnivorous animals are more tolerant of acids than are the herbivora, apparently owing to the greater amount of ammonia which they are capable of forming from their proteid diet. Mankind are capable of dealing with a large quantity of acid in this way.

Excess of acid may occur in the system in two ways: either by failure to excrete that which is normally formed, with resulting accumulation in the blood; or by increased manufacture of acid by chemical processes within the tissues. With regard to the former possibility it is conceivable that lesions of the kidney may at times cause accumulation of toxic substances in cases of diabetes and may thus sometimes precipitate the onset of coma. I alluded in my first lecture to the intense degeneration of the renal tubules which I found in a recent case which died comatose. The sudden onset of coma in some instances could be better understood on such a hypothesis than on that of the gradual accumulation of acids by increased manufacture alone. But such renal lesions are not the invariable rule. In any case the presence of acids appears to be due to formation by the tissues. Von Noorden mentions among acids which may be formed in the body sarcolactic, carbaminic, aliphatic, oxalic, uric, and others, besides those previously mentioned which are most to the fore in diabetes—β-oxybutyric and aceto-acetic (diacetic), related to each other and to acetone.

Coma.—The interest of the series of bodies just alluded to—the acetone series—in diabetes is very great, since it is to one or more of them that attempts have been recently made to assign the causation of diabetic coma. Two older theories may be mentioned as of historical interest. One is that coma is due to a fat embolism of the lungs, arising from the presence of excess of fat in the blood in cases of diabetes. This hypothesis seems untenable for more than one reason. In the first place, liphæmia is not by any means of constant occurrence in diabetes and is not found in all or nearly all cases dying from coma; while it is very doubtful whether fat circulating in the blood in the form of fine droplets, as it does in such conditions, is capable of producing embolism of even capillary vessels, since fat is practically fluid at the temperature of the body and is probably thus able to pass through any vessels to which it is conveyed. The existence of fat-globules in the capillaries of the lungs can, it is true, be demonstrated in some instances; but this is after death when the fat has solidified. There is no proof that the fat has been previously arrested in the capillaries and has thus blocked them. It is not impossible that the lungs may act as the mechanism in such cases for removing excess of fat from the blood, a process of oxidation taking place within them. The second view to which allusion may

be made is that diabetic coma is due to accumulation of carbon dioxide in the blood owing to insufficient absorption of oxygen ; coma would thus be a form of asphyxia. This view seems negatived by the experiments which have been performed to ascertain the respiratory exchange in diabetics. Recently Pembrey, Beddard, and Spriggs have investigated this in cases of diabetic coma and have satisfactorily shown that defective respiratory exchange can be eliminated as a cause of the condition.

To return to the acetone bodies, the first attempt to connect these with diabetic coma was in the direction of identifying acetone with the toxic body at work. This view was sustained by von Jacksch and others. Experimental injection of considerable amounts of acetone into animals and inhalation of this substance gave rise to a condition of stupor and sometimes to glycosuria. On the other hand, acetone can be given in large quantities by the mouth without giving rise to any ill-effects ; and subsequent observers repeating the experiments and studying the production of acetone normally in the body were led to attach little importance to the production of acetonæmia as the cause of coma. Attention was next turned to β-oxybutyric acid as a possible cause, but in the case of this substance also it was found that it could be taken in large amounts without the production of injurious effects ; and that it was tolerated even by animals which had been deprived of their pancreases. Such ill consequences as ever ensue after its administration are now assigned to its acid qualities alone, whereby it withdraws a certain quantity of ammonia from the body to neutralise it (von Noorden). Other authors have laid stress upon the presence in diabetic coma of other acids, especially β-amido-butyric acid ; but it is now generally held that there is no reason to associate any one substance with this condition, which appears to be dependent upon the general fall in the alkalinity of the blood.

Source of acetone bodies.—Now in view of the importance of the acid intoxication which is present in severe cases of diabetes it is necessary to inquire as to the source of the substance by which it is produced. Since aceto-acetic acid and oxybutyric acid are apparently intermediate products which in normal circumstances are excreted as acetone inquiry may conveniently be directed to ascertain the source of this last. In the first place, experimental investigation has shown that the addition of butter to the diet leads to an increased excretion of acetone, so that it would seem likely that it is a product of the disintegration of fat, which is supposed to enter the system practically unchanged by digestive processes. Consumption of other fats may have a similar effect to that produced by butter. In the second place, the chemical composition of the acetone bodies

forcibly suggests an origin from fat, since oxybutyric acid ingested may be excreted as acetone and the relationship of this acid to fat (butter) is sufficiently indicated by its name. A consideration of the chemical formulæ of the substances involved will make the relationship clearer. Glyceryl tributyrate, a typical fat, may be represented as—

$$C_3H_5 . (CH_3 - CH_2 - CH_2 - CO_2)_3.$$

The figures in the brackets represent the formula of butyric acid—

$$H . (CH_3 - CH_2 - CH_2 - CO_2).$$

By substituting in this formula OH for one of the atoms of hydrogen we obtain **β**-oxybutyric acid—

$$H . (CH_3 - CHOH - CH_2 - CO_2).$$

By combination of the two atoms of hydrogen in the second group with one of oxygen aceto-acetic acid and a molecule of water are formed—

$$H . (CH_3 - CO - CH_2 - CO_2) + H_2O ;$$

and by the removal of the last group (CO_2) from this we obtain acetone,

$$CH_3 - CO - CH_3.$$

It would appear, further, that the acetone bodies are formed within the system, not in the intestinal canal, for although small quantities of both acetone and oxybutyric acid have been demonstrated in the contents of the stomach and intestines the administration of purgatives which rapidly clear out the intestinal contents does not diminish the quantity of acetone in the urine; indeed, von Noorden states that it may occasionally even increase it. The acetonuria which occurs in pregnant women is attributed by Stumpf and Stolz to the increased destruction of fat which takes place in the maternal organism and that which sometimes accompanies death of the fœtus has been supposed by Waldvogel to be caused by destruction of fat resulting from the action of toxins absorbed from the uterus. In the absence of evidence to the contrary, then, we are justified in believing that the acetone series of substances is produced within the body from fat. This conclusion appears consistent with the conditions present in the various pathological states in which acetone and its congeners are found to be increased. Thus they are excreted in greatly increased amount in states of starvation in which there is great wasting of the body and in which it has been shown by experiment that the tissue which suffers the most severely is the adipose. A similar explanation would seem to apply to the acetonuria of fevers, of diarrhœal conditions, and of advanced carcinoma, in all of which the fat is suffering serious reduction in quantity. Acetonuria is also seen sometimes as

a result of the administration of anæsthetics. Now the two substances most frequently used for narcosis are ether and chloroform, and both of these are capable of dissolving fat outside the body ; it is only reasonable to suppose that when they are absorbed into the system they may also be capable of acting upon the adipose tissues.

It is true that von Noorden and Mohr deny the possibility of the acetone bodies formed in diabetes resulting from destruction of fat, although they admit that such destruction commonly takes place in this disease. "This factor," they say, "could only explain the excretion of moderate quantities of acetone not the enormous quantities of acetone bodies that severe cases of diabetes frequently eliminate." They do not, however, support this assertion by any evidence and it is not easy to see on what grounds it is founded, since the quantity of fat that is undergoing destruction at any moment in a case of diabetes must, in the present state of our ignorance, be entirely conjectural. The whole of the argument as set forth by von Noorden and Mohr supports the derivation of the acetone bodies from fat, and it is clear that they are formed within the body, not in the alimentary canal. It may be admitted that the acetone could not all be formed from fat used as food ; but there is nothing to show that it is not formed from the fat in the tissues.

Von Noorden attributes the presence of increased acetone in the urine to diminution in the amount of carbohydrate matter in the diet and quotes actual cases in which a great diminution of the acidosis occurred as a result of adding some carbohydrate to the restricted diet of diabetic patients. This is in accordance with the tendency of the present time in the treatment of diabetes not to put patients on so severely restricted a diet as in days gone by ; and there seems no doubt that this procedure constitutes a definite advance ; while the sudden cutting off of carbohydrates from a diabetic's diet has almost certainly before now resulted in the onset of coma. But, on the other hand, all physicians must be acquainted with cases which have exhibited acetonuria when they first came under treatment but which lost this symptom as a sequel of being put upon a more restricted diet (cf. Herter). It seems not impossible that such concomitant conditions as rest in bed may have some influence upon this phenomenon. Von Noorden himself admits that in diabetes the excreted acetone may suddenly decrease and then increase again without reference to the amount of carbohydrate food taken. At the same time it is quite in accord with the theoretical possibilities that defect in carbohydrate food should lead to some increased destruction of the fat in the body, to make up for the loss of a material which is not only important as a source of energy but is probably itself capable of being stored up—if not actually absorbed as Pavy maintains to be usually the case—in the form of fat.

Source of sugar.—Lastly, we have to consider the question of the source of sugar in diabetes. With regard to this question, attention had been chiefly directed to the possibility of the formation of this substance from the different categories of food materials. Thus it seems to have been satisfactorily established that sugar is excreted whether carbohydrate is given or proteid or fat is substituted. From this it is concluded that sugar is formed by the diabetic organism from all these kinds of food. I venture to suggest that to allege these experiments as a proof that all these materials are capable of being converted into sugar is to be guilty of the fallacy of proving too much. Is it not more probable that what is actually occurring is that the diabetic organism is continually forming sugar out of some of its own tissues, and continues to do so whatever kind of food is administered, than that by some extraordinary perversion of chemical change all these diverse materials are converted into sugar? We ought at all events to consider the more simple explanation very carefully before we reject it in order to adopt the more difficult, especially in the presence of the fact upon which I have already insisted to a degree which I fear may become tedious, that in the final stages of diabetes this internal formation of sugar is admitted to occur.

If we inquire what are the tissues which break down into sugar under these conditions the answer is not easy. It is generally assumed that it is the proteid or protoplasmic substance of the body, in view of the fact that the nitrogen excreted in the urine is increased and that this increase is to some extent proportional to the amount of sugar. Recently Baer has published some observations upon the subject, based on experiments made upon dogs poisoned with phloridzin, showing that the quantities of sugar, of acetone, and of nitrogen excreted, if graphically represented, follow very similar curves. Seeing, however, that the acetone is in all probability formed from fat, not from proteids, and yet follows a curve similar to that of the nitrogenous excretion, we have no right to conclude on this ground that the source of the sugar is the proteid of the body. The increased excretion of nitrogen may be connected with the breaking down of proteid as a consequence of the acid intoxication.

Mandel and Lusk also maintain that sugar is derived from proteid, finding in a case which they studied a constant ratio of dextrose to nitrogen in the urine. On the other hand, Lépine states that diabetics may excrete more sugar than is accountable for either by their diet or by destruction of their proteid tissues and concludes that some of the sugar is formed from fat. With regard to this suggestion it may be observed that it seems illegitimate to assume a double source for any substance appearing in the body until it is shown that its presence cannot be accounted for without

such an assumption; in other words we must not lightly suppose the existence of two separate chemical reactions leading to one and the same result until it is shown that neither one alone is sufficient to explain the phenomenon. If some of the sugar is formed from fat, may not it all be thence derived? Theoretical considerations lend considerable support to this suggestion. It the first place, of all the substances within the animal body with the exception of glycogen fat is probably the most nearly allied to sugar. From the point of view of theoretical chemistry the conversion of fat into sugar would seem to present no insurmountable difficulty. The glyccrine radicle of fat may be represented by the formula :—

$$C_3H_5(OH)_3 \text{ or } \left\{ \begin{array}{l} CH_2OH \\ CHOH \\ CH_2OH \end{array} \right.$$

By a series of substitutions of the group CHOH for one of the atoms of hydrogen we might theoretically get a substance :—

$$\left\{ \begin{array}{l} CH_2OH \\ CHOH \\ CHOH \\ CHOH \\ CHOH \\ CHO \end{array} \right\} \text{ or } C_6H_{12}O_6$$

—a typical sugar. Secondly, the production of sugar from fat has been experimentally demonstrated outside the body by Abderhalden and Rona, who showed that if a mixture were made of liver tissue and blood with fats and oils some of these last were converted into sugar. Thirdly, some experiments performed by Lüthje appear to prove that glycerine administered as food to animals may be converted into sugar within the system. It seems certain, therefore, that glycerine formed internally may undergo the same transformation. That a liberation of glycerine takes place in pancreatic disease seems proved by the observation of Cammidge that it may appear in the urine under such conditions. This observation, however, constitutes a somewhat two-edged argument, since if some of the glycerine formed within the body is excrcted unchanged it might be asked why some should be converted into sugar. Fourthly, of the possibility of the conversion of fat into sugar within the body there seems no doubt, since it has been shown that in hibernating animals, such as the marmot —taking no food but merely absorbing a small amount of oxygen—there occurs an increase of the glycogen of the liver, with a corresponding decrease of the fat. The fat must, therefore, have been converted into glycogen, and the further step to sugar is easy.

If the origin of sugar from fat be really existent in

diabetes it is of interest to note that both the substances most characteristic of the disease—the sugar and the acetone bodies—will be derived from destruction of the same tissue, the acetone bodies arising from the fatty acid and the sugar from the glycerine radicle of the fat. It is possible to bring forward various subordinate considerations drawn from the phenomena of natural and experimental diabetes to corroborate the suggestion of a disturbance of fat as the basis of the disease.

1. In the first place, the experiments made by Rosenfeld upon dogs which had been poisoned by phloridzin—experiments to which I have already alluded—suggest a serious disturbance of the adipose tissue in this condition, which is closely similar to diabetes. In phloridzin poisoning it seems possible that the fat is discharged into the blood from the stores of it existing in different parts of the body and is then taken up by the liver. It must, however, be admitted that all the phenomena of phloridzin poisoning are as yet inexplicable upon this or any other theory.

2. That a marked disturbance of the body fat takes place in dogs which have been deprived of their pancreases is shown by some experiments of Lombroso. This observer was investigating the absorption of fat from the intestines in animals in which the pancreas had been removed and he found that more fat was excreted in the fæces than was given in the food; in other words, there existed an intestinal excretion of fat derived from the pre-existing fat in the body. Here, too, it is clear that there must be a breaking down of the adipose tissue within the body of the animals. These two conditions—phloridzin poisoning and removal of the pancreas—are the two most obvious forms of experimental diabetes; the probability that any special lesion which exists in both of them is also present in the natural malady is very considerable.

3. But there are other phenomena pointing this way in diabetes itself. Thus, it is not very rare in it to find that the circulating blood is loaded with fat (liphæmia). This may occur in other conditions but it is most frequently met with in diabetes and is most marked in such cases. It is reasonable to suppose, in view of the conditions just alluded to as existing in experimental animals, that here, too, we have a rapid destruction of fat cells which not only give rise to sugar in the process of disintegration but allow a certain proportion of their contents to escape unchanged into the blood.

4. In starving persons (tramps) and animals glycosuria is frequently met with (Hofmeister, Hoppe-Seyler). Under the same conditions it is found in animals that the fat content of the blood is increased (Fischer). This would appear to be another instance of a condition in which

breaking down of fat is associated with glycosuria, while, as previously mentioned, the acetone in the urine is also increased in starvation, so that the parallel with diabetes is very close.

5. Further, in diabetics it is not rare to find a fatty liver and the kidneys usually contain in their tubules some quantity of fat. Fat is often found lying between the fibres of the muscles. This fat may be simply taken up from the blood in which it exists in excess of the requirements of the tissues.

6. The special cutaneous affection associated with diabetes —xanthoma—appears to consist in an accumulation of fat in the skin.

7. The relationship of diabetes to obesity may perhaps be alluded to in this connexion, though it scarcely affords evidence in favour of the hypothesis. Still the coincidence of the two conditions is of interest. Fat diabetics, as a rule, suffer comparatively little from their malady. It is possible, on the one hand, that many of them are not true diabetics but rather glycosurics. Such patients suffer probably from no pathological destruction of fat due to deficient pancreatic secretion, but they may in presence of the increased amount of fat in their connective tissue produce by its normal disintegration an abnormal amount of sugar; for it is not impossible that the excessive destruction of fat in diabetes—like so many, if not most pathological processes—is only a quantitative change in a normal process; in other words, that some breaking down of fat into sugar is a constantly occurring change natural to the organism, but that it is increased to a harmful extent in diabetes owing to loss of the regulating action of the pancreas. On the other hand, in fat persons who become the subjects of true diabetes, the supply of fat to start with being larger, they will be able to hold out longer against the drain of fat.

8. Lastly, the benefit derived in many cases from the use of fat in the diet may be connected with the destruction of the natural fat of the body produced by the disease.

Each of these indications taken separately amounts to very little, but collectively they may possess a greater weight than the mere arithmetical sum of their individual values. But if diabetes be really due to the action of a poison which causes a breaking down of adipose tissue, it might not improbably also induce some defect in the processes by which these cells assimilate fat. It they are poisoned, they will act less efficiently in the direction of fulfilling all their functions, anabolic as well as catabolic. It may be that in the early stages of the disease the defect is most manifested in defective storage of fat; later, in actual destruction of

existing fat. If this be so, a bond will be established between the alimentary and the composite forms of the malady, without the necessity for the sharp distinction which I emphasised for the sake of the argument in my first lecture.

Of the mechanism, if it be so called, of the storage and distribution of fat little seems to be known. It seems to be established, however, that cells of connective tissue do not directly swallow droplets of fat but that they break down the fat into some soluble material and absorb this, reconstructing fat within their own bodies. In the same way it is stated that in normal circumstances the fat within a cell is not directly discharged into the surrounding fluids, though this occasionally takes place; more often an analysis and a synthesis of the fat are effected, similar in all probability to those by which the process of storage was performed. It is not a very wild conjecture to suppose that the intermediate soluble substance in each process is either sugar or some closely allied substance while the comparatively rare direct discharge of fat from the cell may take place to an excessive extent in cases characterised by the appearance of liphæmia.

I would make no pretence to conceal the fact that the argument which I have set forth with regard to the source of sugar in diabetes is highly speculative and has little actual evidence to support it. It is quite possible, on the other hand, that since the protoplasmic constituents of the body contain both carbohydrate and fatty elements it may be by disintegration of proteid that sugar and even acetone are formed. The parallelism of the excretion of sugar, acetone, and nitrogen seems to point in this direction and the phenomena of phloridzin poisoning and starvation are susceptible of explanation on this basis. Lépine's observations are, however, important. The whole question is one which ime and continued observation and experiment must be left to answer. At present, in spite of the immense amount of work which has been done on this subject, the results are contradictory and inconclusive.

Finally, if diabetes be due to the action of a poison which is normally neutralised by the pancreas, we are in the presence of two factors which interact to produce the disease. It is conceivable that in some cases the poison may be produced in excess of the power of the pancreas to neutralise it, even when the organ is only slightly affected, and that this may be the explanation of some of the cases in which we fail to find noteworthy anatomical changes in it after death. Of the seat of the formation of the toxin we have no indication, but it is not impossible that the benefits derived from restriction of carbohydrate diet arise less from mere limitation of the amount of sugar present in the blood than from the cutting off of the source of the poison which may be derived from carbohydrate metabolism. On the other hand, Dr. Lorand who was good enough to set his views before me in a personal interview, believes

that an excess of animal food in the diet of a diabetic patient is harmful as tending to cause an excessive secretion of the colloid substance of the thyroid gland, this being, in his opinion, the poisonous substance at work. In view of this suggestion it would be interesting to observe carefully cases of obesity which are undergoing a course of treatment by thyroid extract in order to ascertain whether they exhibit glycosuria, but I have not had the opportunity of observing such a case since undertaking this inquiry.

In conclusion, then, I would venture to sum up the views which I have suggested as embodying a possible explanation of the phenomena of diabetes and the arguments by which they were reached.

1. Excess of sugar in the blood, which is the condition precedent of glycosuria, may be caused by over-production of sugar in the system or by diminished use or excretion. There is practically no evidence of either of these last processes. There is convincing evidence that at one stage, at all events, of diabetes there is increased production.

2. Over-production of sugar may depend upon some digestive irregularity, whereby more sugar than normal is poured into the blood from the food or upon manufacture of sugar from the tissues of the body. We have sufficient evidence that both these processes are at work in diabetes, in that at first the output in the urine can be controlled by limiting the diet, whereas later this is not possible. But whereas there are a considerable number of conditions in which sugar appears in the urine apparently as a result of absorption of additional sugar from the alimentary canal—these conditions being identical with diabetes only in the single fact of the appearance of sugar in the urine, while they run an entirely different clinical course—it is in diabetes mellitus alone that we have at any time evidence of formation of sugar from the tissue-cells of the patient. This autolytic formation of sugar, if it may so be called, is the characteristic feature of diabetes in so far as the production of sugar is concerned.

3. It involves less of an assumption to suppose that this autolytic formation of sugar is present in diabetes all through the disease than to suppose that it ensues after a time as a result of the presence in the blood of excess of the very substance—sugar—into which the cells finally break down. The absence of proof of the existence of this process in the early stages of the disease, when the glycosuria is controlled by diet, may be due to the body possessing a certain power of utilising sugar in its nutritive processes, so that only the excess above a definite quantum appears in the urine

4. There is sufficient evidence available to establish beyond the possibility of doubt the fact that there is some connexion between the pancreas and diabetes. Although it is not yet

proved, yet it is becoming increasingly probable that the pancreas is diseased in all cases of diabetes mellitus. An increasing bulk of evidence is also accumulating to show that the function of the pancreas which is in abeyance in diabetes is normally performed by certain special groups of cells known as the islands of Langerhans, which are distinct from the ordinary secreting cells of the gland, but which are not improbably formed from the acini. The special lesion of these islands—hyaline degeneration—which has been associated with diabetes by some writers, is not present in all cases of the disease and may be found (in a less developed state) in other conditions.

5. The action of the pancreas may be exerted in the direction either of supplying a substance necessary for the assimilation of sugar by the cells of the body or in that of counteracting a poison which in some way causes accumulation of sugar in the blood. There is little or no evidence in favour of the former possibility ; in favour of the latter there are the results of experimental intoxication with phloridzin, with suprarenal extract, and with other substances, and a few inconclusive results obtained by injection of secretions derived from diabetic patients.

6. We are not yet in a position to state with any certainty what tissue in the body gives rise to the sugar formed in diabetes. The theoretical possibility that sugar may be derived from fat is supported by certain observations which prove that a serious disturbance of the adipose tissue exists in diabetes. Further, if this hypothesis be admissible a certain unity will be introduced into our conception of diabetes, the phenomena of which will be explicable as manifestations of a single process occurring in a single tissue.

7. Lastly, glycosuria as opposed to diabetes may be due to mere excess of sugar poured into the blood from the alimentary canal in excess of what the system is capable of assimilating ; or it may be due to causes acting analogously to the diabetic puncture of Claude Bernard and leading to a discharge of sugar by the liver from its stores of glycogen.

If the views here set forth are correct it follows that in its earliest stage the diabetic process may constitute rather a predisposing cause of glycosuria than the actual cause of the phenomenon, since the breaking down of the tissue-cells into sugar is at first not more than sufficient to saturate the sugar-assimilating powers of the system. At this stage a slight increase of saccharine food will produce glycosuria—an increase which in a normal person would not have this effect. Similarly a slight nervous shock sufficient to cause the liberation of only a comparatively small quantity of glycogen from the liver would also augment the sugar present in the blood above the

point at which it appears in the urine. In such a way the onset of true diabetes might be ascribed to a shock when in reality it was previously existent but unnoticed. As far as definition is possible, then, diabetes might be defined as an increased internal dissociation of tissue (possibly fat) into sugar, caused by a toxic substance which is produced in the course of normal metabolism and which is normally neutralised by the pancreas.

I venture to think that such an explanation harmonises better than what I may call the alimentary hypothesis with the trend of opinion in the matter of treatment. A comparatively few years ago, on the supposition that the sugar present was the poison at work, it was customary to put patients upon a severely restricted diet and to gauge the progress of the case entirely by the fluctuations in the amount of sugar present in the urine. It is now recognised that such a strict diet as was formerly fashionable is harmful to the sufferer and may even lead to an early appearance of coma. Indeed, the amount of sugar present in the urine is but a fallacious guide in estimating the condition of a patient. It is, perhaps, a criterion of some value when a patient first comes for treatment, as showing the stage which the case has reached and the amount of glycosuria which persists when the patient is on a restricted diet is some measure of the severity of the disease; but a patient taking some carbohydrate food and excreting more sugar may be in a better condition than one on a strict diet excreting a much smaller quantity. Nevertheless, we can hardly doubt that the presence of more than a certain percentage of sugar in the blood must by altering the density of the fluid, if not also in other ways, be detrimental to the organism; and we remain in presence of the old difficulty, how to feed the patient adequately and yet diminish the amount of sugar in the circulation. Nothing seems more certain with regard to the treatment of diabetes than that each patient must be a law to himself and that no general rule can be laid down for guidance. In some cases more and in others less carbohydrate food can be tolerated. The prognosis of any case, however, depends more upon the degree of acid intoxication existing than upon the percentage of sugar in the blood or urine.

I have to thank you, Mr. President and Gentlemen, for your patience in listening to these lectures and can only express my sincere regret that I have not been able to acquit myself more worthily of the responsible task which you did me the high honour of intrusting to me.

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